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OF THE

MEDICAL SCIENCES

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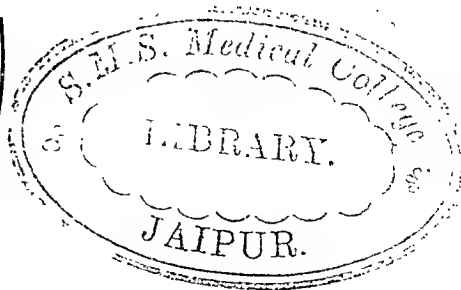
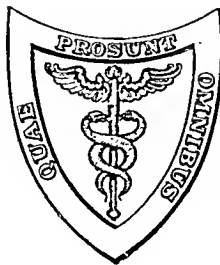
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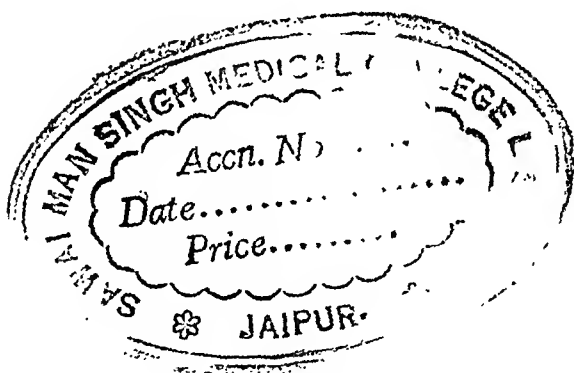
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CONTENTS OF VOL. CLXXX

ORIGINAL ARTICLES

The Effect of Single Massive Doses of Liver Extract on Patients with Pernicious Anemia. By MATTHEW C. RIDDLE, M.D., and CYRUS C. STURGIS, M.D.	1
Erythrocyte Sedimentation. Plasma Fibrinogen and Leukocytosis as Indices of Rheumatic Infection. By A. CARLTON ERNSTENE, M.D.	12
The Value of Blood Bilirubin Estimations in the Differential Diagnosis of Cerebrovascular Accidents. By GARNETT CHENEY, M.D.	24
The Prognostic Value of the Initial Leukocyte and Differential Count in Lobar Pneumonia. By RICHARD MIDDLETON, M.D., and JOHN H. GIBBON, JR., M.D.	31
Aneurysm of the Coronary Arteries. Report of a Case. By RALPH L. COX, M.D., and CHESTER D. CHRISTIE, M.D.	37
The Significance of Sinus Arrhythmia in Old People. By JAMES M. FAULKNER, M.D.	42
The Symptomatology of Arterial Hypertension. By JOSEPH E. F. RISEMAN, M.D., and SOMA WEISS, M.D.	47
Visceroptosis: Its Clinical Significance and Treatment. By EDWARD L. BORTZ, M.D.	59
A Tumor of the Adrenal Gland with Fatal Hypoglycemia. By HORACE B. ANDERSON, M.D.	71
Lipoma of the Mediastinum. By WALLACE M. YATER, A.B., M.S., and E. STUART LYDDANE, B.S., M.D.	79
Alimentary Hyperlipemia. A Study of the Lipemic Curve. By DR. B. HEJDA	84
Atrophy of Subcutaneous Fat Associated with Insulin Injections. By JOHN B. NICHOLS, M.D.	90

A Clinical Study of One Hundred and Three Cases of Scleroderma. By PAUL A. O'LEARY, M.D., and RUBEN NOMLAND, M.D.	95
Studies on the Circulation of the Feet in Diabetes Mellitus with and without Gangrene. By ISAAC STARR, JR., B.S., M.D.	149
Normal Urine Sugar in Cystoscopic Examinations. By RUSSELL RICHARDSON, M.D., and RUTH S. BITTER	171
Diabetic Ketosis and Functional Renal Insufficiency. By ALVIN F. COBURN, M.D.	178
The Problem of Pulmonary Tuberculosis in Patients with Diabetes. By REGINALD FITZ, M.D.	192
Some Observations on Mitral Stenosis and Measurements of Normals Among Chinese. By OTTO WILLNER, M.D.	200
Allergic Migraine. Based on the Study of Fifty-five Cases. By RAY M. BALLYEAT, M.A., M.D., F.A.C.P., and FANNIE LOU BRITTAIN, B.S., M.D.	212
Multiple Aneurysms of the Arteries of the Right Arm Associated with Arteriovenous Fistula and Arterial Embolism. Report of a Case. By DWIGHT L. WILBUR, M.D.	221
Leukopenia Resembling Agranulocytosis with Recovery. By WILLIAM P. THOMPSON, M.D.	232
Psychogenic Factors in the Etiology of Ulcerative Colitis and Bloody Diarrhea. By CECIL D. MURRAY, PH.D.	239
A New Interpretation of the Van den Bergh Reaction. By HIRAM F. SNIDER and JOHN G. REINHOLD	248
Preliminary Notes on Bacteriologic Studies and Treatment of Chronic Epidemic Encephalitis. By WINIFRED BAYARD STEWART, A.M., M.D., and MARY JARDINE EVANS, PH.D.	256
The Futility of Alkali Treatment in Diabetic Coma. Analysis of Forty-seven Cases. By I. I. LEMANN, M.D.	266
Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding. By WILLIAM B. CASTLE, M.D., WILMOT C. TOWNSEND, M.D., and CLARK W. HEATH, M.D.	305
The Normal Filament and Nonfilament Polymorphonuclear Neutrophil Count: Its Practical Value as a Diagnostic Aid. By DAVID L. FARLEY, M.D., HUSTON ST. CLAIR, M.D., and JOHN A. REISINGER, M.D.	336

Note on the Diagnosis of Pneumococcus Peritonitis from the Blood Picture. By CHARLES L. GIBSON, M.D.	344
Studies Concerning Digitalis Therapy in Lobar Pneumonia. By WALTER L. NILES, M.D., and JOHN WYCKOFF, M.D.	348
Barium Chlorid in the Stokes-Adams Syndrome of Complete Heart Block. Negative Results in Eight Cases. By AARON E. PARSONNET, M.D., and ALBERT S. HYMAN, M.D.	356
A Study of Uninfected Mural Thrombi of the Heart. By EARLE A. HARVEY, M.D., and SAMUEL A. LEVINE, M.D.	365
Flarimeter Tests of Circulatory Fitness: A Preliminary Report. By L. F. MACKENZIE, M.D., P. V., WELLS, D.Sc., E. G. DEWIS, M.D., and L. S. YLVISAKER, M.D.	372
The Production of Hypertrophic Arthritis by Interference with the Blood Supply. By ARTHUR D. GOLDBART, V.M.D., LILLIE M. WRIGHT, M.A., and RALPH PEMBERTON, M.D.	386
Subphrenic Abscess. By GATEWOOD, M.D.	398
Remote Symptoms of Unrecognized Thyroid Adenomata. With Low Basal Metabolic Rate Relieved by Operation. By P. K. GILMAN, M.D., and W. E. KAY, M.D.	405
Anorexia Nervosa, Anorexia, Inanition, and Low Basal Metabolic Rate. By JOHN M. BERKMAN, M.D.	411
Clinical and Pathological Studies on So-called Tubular Nephritis (Nephrosis). By S. BURT WOLBACH and KENNETH D. BLACKFAN	453
Transfusion of Blood in Bright's Disease. By HERMAN O. MOSENTHAL and BENJAMIN ASH	476
The Etiology of Erythema Nodosum in Children. Its Relation to Early Tuberculous Infection. By LLOYD B. DICKEY, M.D.	489
Antistreptococcus Serum Treatment of Patients with Rheumatic Fever. By C. H. HITCHCOCK, M.D., CURRIER McEWEN, M.D., and HOMER F. SWIFT, M.D.	497
Blood Transfusion in the Acute Infectious Diseases. An Analysis of 100 Cases. By JOHN FITCH LANDON, M.D.	514
On Some Venous Murmurs Found in Hepatic Cirrhosis and Their Confusion with Murmurs of Congenital Heart Disease. By NORMAN B. GWYN, M.D.	525

Observations Upon Chronic Cholecystitis. With Special Reference to Motor Disturbances of the Gastrointestinal Tract in Relation to Preoperative and Postoperative Symptoms. By NOBLE W. JONES and DORWIN L. PALMER. With Chemical Studies by R. B. ADAMS.	531
A Clinical Study of Visceroptosis. By BLANTON P. SEWARD, A.B., M.D.	548
Observations on Visceral Pain. By R. D. RUDOLF and A. G. SMITH	558
Treatment of Pernicious Anemia with Desiccated, Defatted Stomach. By CYRUS C. STURGIS, M.D., and RAPHAEL ISAACS, M.D.	597
The Treatment of Pernicious Anemia with an Extract of Fish Liver. By JOSEPH E. CONNERY, M.D.	603
Mitosis in Myeloblasts in Peripheral Blood. By WILLIAM A. GROAT, B.S., M.D.	607
Radiation Therapy of Polycythemia Vera. By GEORGE T. PACK, M.D., and LLOYD F. CRAVER, M.D.	609
The Effect of Amyl Nitrite on the Size of the Heart and the Width of the Aortic Shadow as Determined Roentgenologically. By WILLIAM A. BRAMS, M.D., and HERMAN A. STRAUSS, B.S.	618
Streptococcus Viridans Endocarditis in Children. Report of Fifteen Cases and of One Instance of Streptococcus Viridans Septicemia Without Endocarditis. By CLIFTON B. LEECH, M.D.	621
Auricular Fibrillation and Flutter in Metastatic Growths of the Right Auricle. By ARTHUR M. FISHBERG, M.D.	629
Analysis of Nine Hundred and Eighteen Cases of Bacillary Dysentery Treated with Specific Serum. By PEDRO T. LANTIN, M.D., D.T.M.	635
Bacterial Hypersensitivity of the Intestinal Tract. Its Treatment with Autogenous Vaccine and Sodium Ricinoleate. By STANLEY E. DORST, A.B., M.D., and ROGER S. MORRIS, A.B., M.D.	650
A Clinical Study of Gumma of the Liver. By JULIUS FRIEDENWALD, M.D., and THEODORE H. MORRISON, M.D.	656
Renal Glycosuria with Ketosis During Surgical Complications. By FRANK N. ALLAN, M.D., and FRANCES R. VANZANT, M.D.	670
Acute Interstitial Pancreatitis in Two Cases of Diabetic Coma. By ALVIN G. FOORD, M.D., and BYRON D. BOWEN, M.D.	676
The Adrenalin Test and Cholesterol Determination in the Diagnosis of Borderline Hyperthyroidism. By J. WILLIAM HINTON, M.D., F.A.C.S.	681

Some Problems in the Diagnosis and Treatment of Thyrotoxicosis. By FRED E. BALL, M.D.	687
Low Basal Metabolism Following Lobar Pneumonia Associated with Marked Undernutrition. By A. H. GORDON and I. M. RABINOWITCH .	695
Metastatic Abscesses of the Brain. A Clinical Study. By HARRY L. PARKER, B.A., M.B.	699
Roentgenology of the Thymus in Infancy and Differential Diagnoses of Enlarged Thymus and Its Treatment. By HENRY K. PANCOAST, M.D.	745
Remarks on the Pathogenesis of Graves' Disease. By DAVID MARINE, M.D.	767
The Size of the Heart in Goiter. A Teleroentgenographic Study. By LEWIS M. HURXTHAL, M.D., O. J. MENARD, M.D., and M. E. BOGAN, M.D.	772
Edema. By HERMAN ELWYN, M.D.	781
Gastric Hemorrhage Due to Familial Telangiectasis. By L. NAPOLEON BOSTON, A.M., M.D.	798
The Effect of Liver Extract on the Blood of Normal Persons. By MARTIN P. CRANE, M.D., ISABEL HOWARD, and WILLIAM P. MURPHY, M.D.	803
The Influence of Gastric Juice on Erythropoiesis in Pernicious Anemia. By WILLIAM S. MIDDLETON, M.D., and R. H. STEHM, M.D. . .	809
Incidence of the Sickle-cell Trait in Industrial Workers. By G. M. BRANDAU, B.A., M.D.	813
Chlorotic Anemia of Pregnancy. A Report of Three Cases. By MAURICE B. STRAUSS, M.D.	818
Epituberculosis. A Study of Ten Cases for a Period of Over Two Years. By BENJAMIN GOLDBERG, M.D., F.A.C.P., and BENJAMIN M. GASUL, M.D.	824
The Protective Power of the Pleura. By MINAS JOANNIDES, M.S., M.D., F.A.C.S.	833
The Ocular Manifestations of Sympathetic Nervous System Hyperactivity in Conditions Other than Exophthalmic Goiter and Especially in Essential Hypertension. "Lidspasm:" A New Eye Sign. By HARRY B. FRIEDGOOD, M.D.	836

REVIEWS

Reviews of Books	113, 272, 425, 569, 712, 849
Books Received	117, 277, 427, 574, 717, 855

PROGRESS OF MEDICAL SCIENCE

Medicine	119, 279, 430, 576, 719, 857
Surgery	120, 281, 431, 578, 721, 859
Therapeutics	122, 283, 433, 580, 724, 860
Pediatrics	124, 285, 435, 582, 726, 862
Dermatology and Syphilis	127, 288, 438, 585, 729
Gynecology and Obstetrics	128, 289, 439, 586, 730, 865
Ophthalmology	130, 291, 440, 732
Oto-Rhino-Laryngology	131, 293, 441, 588, 734, 866
Radiology	133, 295, 443, 590, 735, 867
Neurology and Psychiatry	136, 298, 446, 591, 869
Pathology and Bacteriology	137, 303, 447, 593, 739, 871
Hygiene and Public Health	139, 300, 449, 594, 741, 872
Physiology	142, 874

THE
AMERICAN JOURNAL
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JULY, 1930

ORIGINAL ARTICLES.

THE EFFECT OF SINGLE MASSIVE DOSES OF LIVER EXTRACT
ON PATIENTS WITH PERNICIOUS ANEMIA.

MATTHEW C. RIDDLE, M.D.,

JUNIOR ASSISTANT IN RESEARCH, THE THOMAS HENRY SIMPSON MEMORIAL INSTITUTE
FOR MEDICAL RESEARCH; FELLOW IN MEDICINE, NATIONAL RESEARCH COUNCIL,

AND

CYRUS C. STURGIS, M.D.,

PROFESSOR OF MEDICINE, UNIVERSITY OF MICHIGAN; DIRECTOR, THE THOMAS HENRY
SIMPSON MEMORIAL INSTITUTE FOR MEDICAL RESEARCH; DIRECTOR,
DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY HOSPITAL.

(From the Thomas Henry Simpson Memorial Institute for Medical Research,
Ann Arbor, Michigan.)

IN 1926 Minot and Murphy demonstrated¹ that, when sufficient amounts of liver were included in the diet of patients with pernicious anemia, prompt and enduring remissions invariably occurred. Later, aided by Cohn² and others, they showed that the active substance in liver which produces this effect can be extracted from liver in concentrated form. Now various extracts of liver, which contain in small bulk its therapeutic value, are available for general use. Such liver extracts have obvious practical advantages in the study and treatment of pernicious anemia, since, freed from most of the substances present in liver, the potent material can easily be administered in concentrated form in large amounts. The customary dosage of liver given to patients with pernicious anemia is that originally recommended by Minot and Murphy,¹ that is, 125 to 240 gm. daily. If liver extract is used, somewhat larger daily doses (extract derived from 300 to 600 gm. of fresh liver) are ordinarily required.

Minot, Murphy, Cohn and their associates² have also studied the relation of the amounts of liver extract used to the reticulocyte response and find that when the extract derived from 300 gm. of liver is administered daily a satisfactory response is produced. If a greater amount of extract (from 600 gm. of liver) is given daily, the response is similar in magnitude but occurs more rapidly. If lesser amounts of extract are used the rise in the percentage of reticulocytes may occur but is less in magnitude, is more delayed and is more prolonged. They believe that "within certain limits the response tends to depend upon the total amount of extract given rather than the daily dose."

This observation and the experience of Bloomfield³ who produced a complete remission in a patient with sprue with a single large dose of liver extract suggested the study of the effects of single, massive doses of liver extract in pernicious anemia which is reported in this paper.

Material and Methods. The effects of single, massive doses of liver extract were studied intensively in 4 patients with typical pernicious anemia over periods of from twenty-two to thirty-seven days. In 3 patients a single dose of thirty vials of Lilly's liver extract No. 343 (equivalent to 3000 gm. of liver) was given. To the fourth patient half this amount or fifteen vials of liver extract was used as a single dose. No further medication was given to any of these patients until the resultant reticulocyte response was completed.

The required amount of liver extract, dissolved in 200 or 300 cc. of water, was usually given by stomach tube since in such large amounts liver extract taken by mouth is extremely nauseating and cannot be retained when swallowed. Even when introduced by stomach tube considerable amounts of liver extract, mixed with gastric juice and saliva, were vomited within a half hour. When this occurred the vomited material was filtered and returned by stomach tube, and was retained. Following the administration of the liver extract in this fashion, the patients complained of nausea and a sensation of fullness in the epigastrium which disappeared within an hour as the patient lay quietly in bed. As these symptoms disappeared there was increased intestinal activity, followed by a profuse watery diarrhea in about an hour. After the passage of several liquid stools no further discomfort was experienced. Except for the transitory nausea and diarrhea, no ill effects from these very large doses of liver extract were observed.

Observations on the changes occurring in the blood were made at frequent intervals. In 3 patients the percentage of reticulocytes was estimated at four-hour intervals day and night during the reticulocyte response; in the fourth patient at twelve-hour intervals. The numbers of red blood cells and white blood cells were counted and the amount of hemoglobin in the blood was determined at

least every twelve hours and in one patient every four hours. The changes in the microscopic character of the various types of blood cells were also carefully studied at intervals of four to twelve hours.

All estimations were performed with standardized instruments and with the usual precautions to insure accuracy.

Case Reports. Each patient gave a characteristic history of pernicious anemia and the physical and laboratory findings were typical of this disease. In every patient the characteristic response and improvement of blood followed liver medication.

CASE A.—Mr. H. R., aged sixty-three years, entered the hospital during a second relapse on May 14, 1928. The initial blood findings were: Red blood cell count, 2,370,000 per c.mm.; white blood cell count, 2120 per c.mm.; hemoglobin, 57 per cent (Sahli). On May 16 he was given fifteen vials of Lilly's liver extract No. 343 at 8 P.M. by stomach tube. No further medication was given until May 29, when daily doses of thirty capsules of Abbott's liver extract were begun. At the time of discharge, June 4, 1928, the blood findings were: Red blood cell count, 3,780,000 per c.mm.; white blood cell count, 9850 per c.mm.; hemoglobin, 77 per cent (Sahli).

CASE B.—Mr. A. B., aged fifty-four years, was studied during his first relapse. On entering the hospital, May 17, 1928, his initial blood findings were: Red blood cell count, 1,870,000 per c.mm.; white blood cell count, 5600 per c.mm.; hemoglobin, 50 per cent (Sahli). On May 18, at 4 P.M., thirty vials of Lilly's liver extract No. 343 were administered by stomach tube. No further medication was given until May 30, when four vials of Lilly's liver extract No. 343 were given daily. When discharged, June 12, 1928, the blood findings were: Red blood cell count, 2,670,000 per c.mm.; white blood cell count, 8300 per c.mm.; hemoglobin, 75 per cent (Sahli).

CASE C.—Mr. J. R., aged fifty-five years, was studied during his third relapse. On May 8, 1928, before treatment the blood findings were: Red blood cell count, 1,430,000 per c.mm.; white blood cell count, 3300 per c.mm.; hemoglobin, 32 per cent (Sahli). On May 8, at 8 A.M., thirty vials of Lilly's liver extract No. 343 were given by stomach tube. No further medication was given until May 25, when at 4 P.M., a second dose of thirty vials of Lilly's liver extract No. 343 was administered by stomach tube. On June 2 the daily administration of four vials of Lilly's liver extract No. 343 was begun. When he was discharged on June 20, 1928, the blood findings were: Red blood cell count, 3,910,000 per c.mm.; white blood cell count, 6000 per c.mm.; hemoglobin, 76 per cent (Sahli).

CASE D.—Mr. B. P., aged forty-two years, entered the hospital on May 18, 1928, during his second relapse, in a semicomatose condition. The initial blood findings then were: Red blood cell count, 690,000 per c.mm.; white blood cell count, 4900 per c.mm.; hemoglobin, 15 per cent (Sahli). On May 19, at 8 A.M., he was given thirty vials of Lilly's liver extract No. 343 by stomach tube. No further medication was given until June 1, when daily doses of thirty capsules of Abbott's liver extract were begun. When discharged on June 20, 1928, his blood findings were: Red blood cell count, 2,400,000 per c.mm.; white blood cell count, 6250 per c.mm.; hemoglobin, 42 per cent (Sahli).

Clinical Effects of a Single Massive Dose of Liver Extract. The immediate clinical response of patients with pernicious anemia to

the administration of a single, massive dose of liver extract compares favorably with that obtained when adequate smaller daily doses are given. The increase of appetite, strength and sense of well being, and the decrease of pallor and icterus are similar in either case although improvement begins somewhat earlier following the administration of massive single doses. Ordinarily, when three to six vials of liver extract are given daily, evidence of clinical improvement is seen in from three to four days after liver medication has been started. Patients receiving a single dose of thirty vials of liver extract begin to show clinical improvement after two days. One patient (Mr. B. P.), who was semicomatose and, being nauseated, was unable to retain food, regained consciousness and appetite within twenty-four hours after the administration of thirty vials of liver extract.

The Reticulocyte Response to Single Large Doses of Liver Extract. The reticulocyte response to liver treatment in patients with pernicious anemia serves, as Minot² has emphasized, as a valuable index of the effectiveness of treatment, and is therefore, from a practical standpoint, a most important feature of early remission. The nature of this response and the important factors influencing it are well known to consist of a rise and a subsequent fall in the numbers and the percentage of erythrocytes containing reticulum during the first two weeks of liver treatment. The important features of the reticulocyte response are its magnitude and the rate at which it takes place.

The magnitude of the response is measured either by the concentration of reticulocytes (million per c.mm. of blood) when their percentage is greatest or by the maximum percentage of reticulocytes observed during the reticulocyte response. Minot and his associates,² by studying the data obtained from groups of patients with varying degrees of anemia, have made the observation, which has been confirmed by others, that the magnitude of the reticulocyte response varies inversely with the red blood cell count before treatment. They have found empirically that the relationship between the red blood cell count of the patient before treatment (E_o), and the expected maximum concentration of reticulocytes (E_{pr}) in millions per cmm. of blood can be expressed by the formula: $E_{pr} = 0.73 - 0.2 E_o$. In our experience this formula is satisfactory, and may be used to determine whether treatment in any given case has been efficient.

The rate at which changes in the percentage of reticulocytes occur is measured by the time intervals between the first administration of liver and the beginning, peak, and end of the increase of reticulocytes. Ordinarily the reticulocytes begin to increase about three days after treatment begins, rise to their greatest numbers on the seventh or eighth day, and return to a normal percentage (approximately 2 per cent) in about two weeks if the daily dosage

of liver is 300 gm. or an equally effective amount of liver extract. If larger amounts of liver material are given, these changes tend to occur earlier. The first rise in percentage may appear as early as the second day, the maximum percentage by the fifth or sixth day, and the end of the increase by the tenth or twelfth day if maximal amounts of liver (600 gm. or more) or liver extract are used daily.

Judged by these standards the reticulocyte responses obtained after the administration of single, massive doses of liver extract, were satisfactory in the 4 patients studied. The significant data are shown in the table. That the response obtained in each case was approximately of the expected magnitude may be seen by a comparison of the concentration of reticulocytes observed at the peak of the reticulocyte rise and the concentration estimated by the formula: $E_{pr} = 0.73 - 0.2 E_o$.

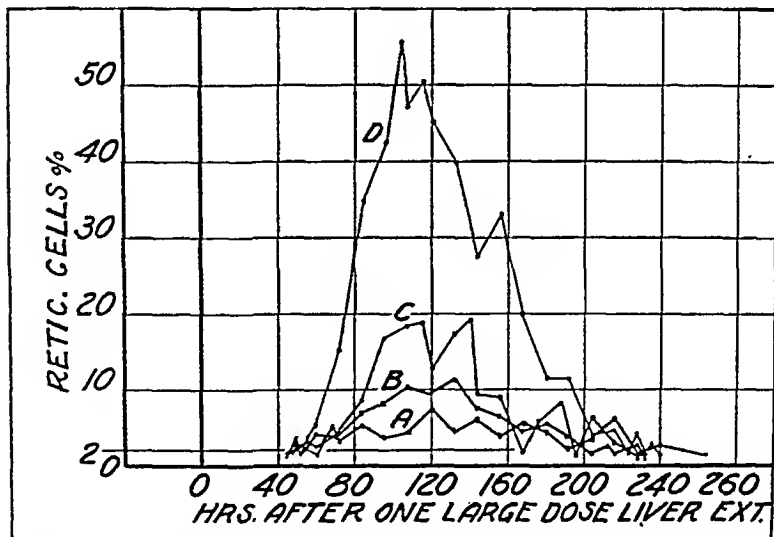
EFFECTS OF SINGLE MASSIVE DOSES OF LIVER EXTRACT.

Patients.	A. Mr. H. R.	B. Mr. A. B.	C. Mr. J. R.	D. Mr. B. P.
RED BLOOD CELL COUNT, MILLIONS PER C.M.M.				
Before treatment (E_o) . . .	2.37	1.87	1.43	0.69
At peak of retic. rise (E_p) . .	2.86	2.41	1.99	1.12
End of retic. response . . .	3.56	2.71	2.11	1.57
HEMOGLOBIN (SAHLI).				
Before treatment . . .	57	50	32	15
At peak of retic. rise . . .	66	52	47	20
End of retic. rise . . .	70	61	47	35
WHITE BLOOD CELL COUNT, PER C.M.M.				
Before treatment . . .	2120	5600	3300	4900
At peak of retic. rise . . .	9100	7500	4600	6150
End of retic. rise . . .	9600	7100	4350	5850
RETICULOCYTE RESPONSE.				
Maximum percentage (R) . . .	7.5	11.4	19.4	55.7
Maximum concentration (observed), millions per c.m.m. (E_{pR}) . . .	0.215	0.275	0.386	0.624
Maximum concentration (calculated), 0.73 to 0.2 (E_o)	0.256	0.356	0.444	0.592
Increase begins (hours after treatment)	48	48	52	48
Increase maximum (hours after treatment)	120	132	140	104
Increase ends (hours after treatment)	240	228	236	228
Duration retic. increase (hours)	192	180	184	180
DOSAGE OF LIVER EXTRACT.				
Vials of liver extract (one vial 100 gm. liver) . . .	15	30	30	30

The rate of the reticulocyte response was remarkably constant in the 4 patients studied. The first rise in the percentage of the reticu-

locytes above 2 per cent, the upper limit of normal, was seen forty-eight hours after the administration of the liver extract in 3 patients and in fifty-two hours in the fourth. The highest percentage of reticulocytes occurred between one hundred and four and one hundred and forty hours after the administration of the large dose of liver extract. The last elevated reticulocyte figure (that is, the end of the reticulocyte response) was seen between two hundred and twenty-eight and two hundred and forty hours after liver extract was given. The duration of the elevated reticulocyte percentage varied between one hundred and eighty and one hundred and ninety-two hours in the 4 cases. In terms of days, the response of the reticulocytes began at the end of two days, reached a maximum in five or six days, and was ended during the tenth day after the administration of a single large dose of liver extract, the rate of the response being that which is seen under the most favorable circumstances when liver extract is given in large daily doses. The remarkable constancy of the response in these 4 patients is shown graphically in Chart I.

CHART I.—DURATION AND MAGNITUDE OF RETICULOCYTE RESPONSE AFTER A SINGLE LARGE DOSE OF LIVER EXTRACT WITH VARYING DEGREES OF ANEMIA BEFORE TREATMENT.



A, Patient A; B, Patient B; C, Patient C; D, Patient D. (See table.)

The percentages of reticulocytes, when measured every four hours, showed certain variations. Minor fluctuations up or down often were seen, which apparently had no significance and were considered to be chance variations incident to the measurement of the percentage of reticulocytes. As contrasted to these chance variations a fairly regular daily variation of the percentage of

reticulocytes was observed except during a rapid increase or decrease in their numbers. Similar daily variations have been observed by Porter and Irving.⁴ Thus, during a twenty-four hour period, the highest percentages of reticulocytes most often occurred at night, usually at midnight or 4 A.M., and the lowest percentages in the daytime, usually between 8 A.M. and 4 P.M. with the patients at rest in bed. During the reticulocyte response the numbers of reticulocytes may increase or decrease greatly within a four-hour period. When rapidly changing in numbers, the reticulocyte percentage sometimes fell or rose as much as 20 per cent within four hours when the reticulocyte response was great, as in patient B. P.

"Blast Crises." The finer microscopic changes in the blood cells of the 3 patients who received thirty vials of liver extract in a single dose, were studied carefully for each four-hour period during the early part of the remission. In all 3 there occurred a so-called "blast crisis" similar to those observed by Minot² in patients receiving daily doses of liver. In each patient immature forms of both red and white blood cells appeared in the blood smears shortly after the administration of liver extract.

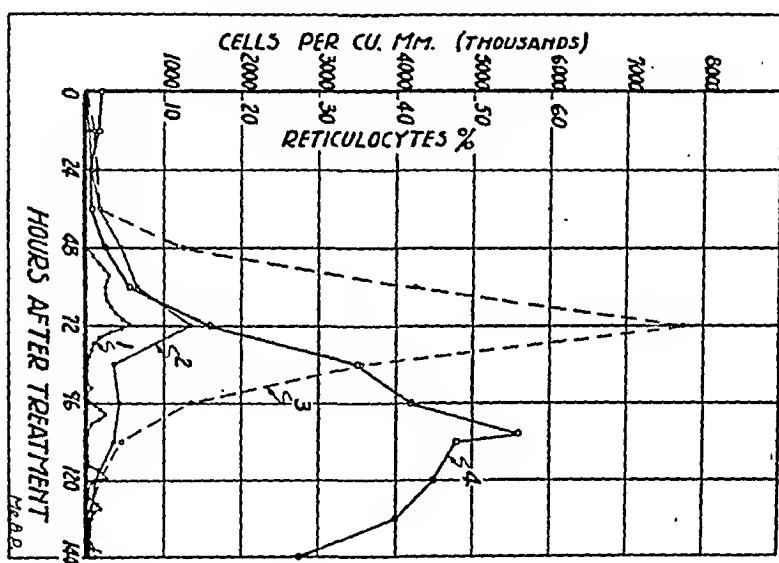
In patients A. B. the first nucleated red blood cells to appear were megaloblasts. These first appeared sixteen hours after the administration of the large dose of liver extract. They then gradually disappeared being replaced by normoblasts at thirty-two hours. By the forty-eighth hour after the administration of liver extract only an occasional nucleated red blood cell could be found and the numbers of the reticulocytes began to increase. Myelocytes appeared simultaneously with the megaloblasts and at thirty-two hours formed 5 per cent of the total number of white blood cells. Myelocytes were present in small numbers as late as fifty-two hours after the administration of the liver extract.

In patient J. R. megaloblasts and myeloblasts were present eight hours after the liver extract was given. They increased in numbers until the thirty-sixth hour when normoblasts and myelocytes were seen. The megaloblasts then decreased in numbers as the normoblasts increased. Nucleated red blood cells and immature white blood cells of myeloid origin persisted for sixty hours after the administration of liver extract although with appearance of increased numbers of reticulocytes beginning at forty-eight hours these cells were found only occasionally. In both patients other evidences of immaturity, such as Howell-Jolly bodies and Cabot ring bodies were occasionally noticed in red blood cells during the period of the "crisis."

A most remarkable "crisis" occurred in patient B. P. whose red blood cell count before treatment was 690,000 per c.mm. Megaloblasts, normoblasts and myelocytes were observed in the blood twelve hours after the administration of liver extract (Chart II). Myeloblasts were present at twenty-four hours. The numbers of

the nucleated red blood cells and immature white blood cells increased to reach their maximum numbers seventy-two hours after the giving of the liver extract, decreasing rapidly in numbers thereafter. They were present in small numbers as late as one hundred and forty-four hours after the administration of liver extract. Hemohistioblasts appeared at forty-eight hours, reached a maximum number at seventy-two hours and were present in small numbers as late as one hundred and fifty-two hours after the giving of liver extract. At seventy-two hours the point at which the "crisis" was at its maximum, myelocytes were present in a concentration of 973 per c.mm. of blood, myeloblasts in a concentration

CHART II.—UNUSUAL CRISIS OF IMMATURE MYELOID CELLS AFTER LARGE DOSE OF LIVER EXTRACT.



1. Numbers of hemohistioblasts per cubic millimeter of blood. 2. Numbers of immature myeloid white blood cells (myelocytes and myeloblasts) per cubic millimeter. 3. Numbers of nucleated red blood cells (megaloblasts and normoblasts) per cubic millimeter. 4. Percentage of reticulocytes.

of 343 per c.mm., hemohistioblasts 548 per c.mm. and nucleated red blood cells 7746 per c.mm. Among the nucleated red blood cells the megaloblast was the dominant type of cell during the early part of the "crisis;" the normoblast during the later part. Other peculiar forms of immature red blood cells were seen during this period of intense hematopoietic response, Cabot ring bodies, Howell-Jolly bodies and Isaacs' granules and in a few instances red blood cells exhibiting mitotic figures being observed.

In these 4 patients it is interesting to point out that immature myeloid cells appeared in considerable numbers preceding the increase in numbers of reticulocytes. Blast crises have been observed

to occur spontaneously in patients with pernicious anemia, but as Minot² has suggested, the crises following the stimulation of the bone marrow by liver have a different significance than those developing spontaneously. Spontaneous blast crises in pernicious anemia have in some instances been regarded as an unfavorable sign which precedes death and as an evidence of bone marrow failure. The blood crises following liver medication, such as those described above, seem to be evidence of an intense stimulation of the bone marrow to hematopoietic activity and have a favorable rather than an unfavorable significance.

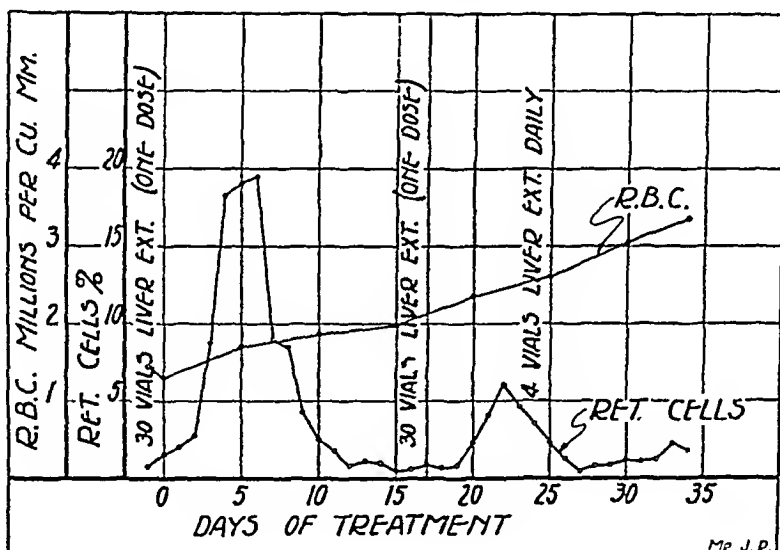
Increase of Numbers of Red and White Blood Cells and of Amount of Hemoglobin. As may be seen in the table there was a satisfactory increase in the red blood cell counts with a gain in number of red blood cells per cubic millimeter varying from 680,000 to 1,190,000 in different patients during the ten-day period following the administration of a large dose of liver extract. A similar satisfactory increase in the amounts of hemoglobin was also observed.

The white blood cell counts at the end of the ten-day period after liver extract administration were essentially at the same level as before treatment but under further medication increased to a normal level by the end of the period of observation in each case. Three patients showed leukocytosis during the reticulocyte response. One patient (B. P.) had an elevated white count beginning forty-eight hours after the liver extract administration which lasted for two days reaching a maximum of 14,250 per c.mm. at seventy-two hours. This period of leukocytosis accompanied the "blast crisis" described above. Patient H. R. had an elevated white blood count sixty and seventy-two hours after the administration of liver extract, the highest value being 13,200 per c.mm. In patient A. B. the white blood cell count one hundred and seventy-two hours after the administration of liver extract was 12,450 per c.mm., the leukocytosis lasting twelve hours. The fourth patient showed no elevation of the white blood cell count during the period of observation. In these patients the leukocytosis apparently developed as a part of the bone marrow response rather than as a response to infection since none showed evidence of a complicating infective process during the period of observation.

Duration of the Effect of a Single Massive Dose of Liver Extract. While a large single dose of liver extract may, as has been shown, produce a very satisfactory reticulocyte response, the effect is not lasting. After a sufficient interval of time, if more extract is given, a second reticulocyte response may be produced, the magnitude of which depends upon the time elapsing after the initial dose. Patient J. R. was given a second dose of thirty vials of liver extract seventeen days after the first had been given. A second reticulocyte response was produced, the highest percentage of the reticulocytes following the second dose of extract being 6.0 on the fifth day (Chart III).

Eight days after the second large dose of liver extract, daily doses of four vials of liver extract were given without further elevation of the reticulocyte percentage. From this evidence the effect of thirty vials of liver extract appears to persist for eight days but not for seventeen days. Patient B. P. was given the equivalent of 300 gm. of liver daily in the form of liver extract twelve days after the original dose of thirty vials of liver extract and showed a reticulocyte response with a maximum reticulocyte percentage of 5.7 on the eighth day. In this case the effect of thirty vials of liver extract lasted less than twelve days. A third patient, A. B., was given four vials of liver extract twelve days after the original dose of liver extract and showed a reticulocyte response in which the maximum reticulocyte response of 3.1 per cent was reached on the

CHART III.—DURATION OF THE EFFECT OF SINGLE DOSES OF 30 VIALS OF LIVER EXTRACT.



eighth day. From these figures it seems probable that the effect of thirty vials of liver extract lasts in the neighborhood of ten days, the average dose being three vials of liver extract per day. This is in accordance with the findings observed when daily doses of liver extract are used, three vials per day being the minimum dose giving satisfactory results.

Summary. 1. The observed effect of single large doses of liver extract on patients with pernicious anemia confirms the opinion, expressed by Minot, that the response to liver medication depends rather on the total amount of the active liver principle used during a certain period of time rather than on the amount consumed each day. A similar effect is obtained from the thirty vials of liver extract given in a single dose or in 10 doses of three vials each at daily

intervals. The active liver principle seems to be utilized in a quantitative fashion, the effect of a given amount lasting a given time, the minimum daily amount sufficient for a satisfactory response being that present in three vials of liver extract (approximately equivalent to $\frac{1}{2}$ pound of liver).

2. The magnitude of the reticulocyte response does not appear to be influenced by the presence within the body of an excessive amount of the active liver principle, a certain maximum number of reticulocytes being possible in any case, the number being related to the original blood level.

3. The rate of the reticulocyte response appears to be accelerated to a certain extent by the dosage of the liver extract, the response occurring most rapidly when a large, single dose or large daily doses of liver extract are given. When the reticulocyte response develops at a maximum rate, as it apparently does after the administration of a single dose of thirty vials of liver extract, reticulocytes begin to increase in numbers and percentage about forty-eight hours after the giving of the liver extract. A maximum number and percentage of reticulocytes appears between one hundred and four and one hundred and forty hours after the administration of liver extract and the reticulocyte response ends within two hundred and forty hours.

4. That the administration of a single dose of thirty vials of liver extract has an intensely stimulating effect upon the hematopoietic tissues of the bone marrow is indicated by the presence of numerous nucleated red blood cells and immature white blood cells of myeloid origin in the blood during the first two or three days after the liver extract is given.

5. The immediate clinical effects, reticulocyte response and increase in the red blood count and the amount of hemoglobin in the blood are as satisfactory after a single dose of thirty vials of liver extract as when three vials doses are given daily for ten days. The effect of a single dose of thirty vials lasts approximately ten days.

BIBLIOGRAPHY.

1. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, *J. Am. Med. Assn.*, 1926, **87**, 470.

2. Cohn, E. J., Minot, G. R., Fulton, J. F., Ulrichs, H. F., Sargent, F. C., Weare, J. H., and Murphy, W. P.: The Nature of the Material Effective in Pernicious Anemia (I), *J. Biol. Chem.*, 1927, **74**, 69. Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia (II), *J. Biol. Chem.*, 1928, **77**, 325. Minot, G. R., Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy, *AM. J. MED. SCI.*, 1928, **175**, 581. Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A.: The Treatment of Pernicious Anemia with Liver Extract: Effects upon the Production of Immature and Mature Red Blood Cells, *AM. J. MED. SCI.*, 1928, **175**, 599.

3. Bloomfield, A. L., and Wyckoff, H. A.: Treatment of Sprue with Liver Extract, *AM. J. MED. SCI.*, 1929, **177**, 209.

4. Porter, W. B., and Irving, H.: Reticulocytosis Produced by Liver Extract, *Arch. Int. Med.*, 1929, **44**, 502.

ERYTHROCYTE SEDIMENTATION, PLASMA FIBRINOGEN AND LEUKOCYTOSIS AS INDICES OF RHEUMATIC INFECTION.

By A. CARLTON ERNSTENE, M.D.,

ASSISTANT IN MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Boston City Hospital, the Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.)

THE administration of salicylates to patients with rheumatic fever frequently causes prompt subsidence of the fever and polyarthritis. The occasional recrudescence of these symptoms on discontinuing medication indicates that the symptomatology rather than the underlying infection has been altered by the drugs and that these symptoms alone cannot be utilized as indices of the course of the disease. This fact frequently is overlooked, and, as a result, many patients are allowed out of bed before the infection has subsided. It is probable that such an error, in many instances, prolongs the total duration of the disease by favoring renewed activity of the infection and increases the amount of permanent cardiac damage suffered by the patient. Because of these difficulties all possible indices of the activity of the underlying infection should be investigated.

Swift, Miller and Boots¹ have directed attention to the significance of the leukocyte curve in rheumatic fever. Their studies demonstrate that, in the absence of nonrheumatic infection, a persisting leukocytosis indicates activity of the rheumatic infection. Conversely, repeated white blood cell counts below 9000 per c.mm., after the discontinuance of antirheumatic drugs, signify that the disease is nearing its end.

It is known that in rheumatic fever at the height of the disease the rate of sedimentation of the red blood cells is greatly accelerated. Herrmann,² in a study of 46 patients, observed that the sedimentation rate returned to normal more slowly than the temperature and leukocyte count. Kahlmeter³ and Sharpless⁴ have made similar observations, and Kahlmeter³ has stated that the rheumatic infection cannot be considered terminated until the sedimentation rate has become normal. The work of these investigators is subject to the following criticisms: (1) None of the observers presented simultaneous measurements of the sedimentation rate and leukocyte count throughout the course of the disease. (2) In measuring the sedimentation rate the blood specimens were diluted with a solution of sodium citrate; this dilution makes accurate measurements impossible.⁵ (3) No attempt was made to correct the results for variations in the cell-volume percentage of the blood specimens

employed. It is, therefore, impossible to state to what extent the rapid rate found by these investigators was due to the anemia which often accompanies rheumatic fever.

Rourke and Ernstene⁶ recently reported a method by which a correction can be made for the accelerating effect of anemia on the sedimentation rate. The corrected rate (corrected sedimentation index) obtained in this manner gives more accurate information regarding the presence of infection or tissue damage in the body than do rates obtained by older methods. The present study was undertaken to learn whether the corrected sedimentation index might be a reliable criterion of the underlying activity of the infection in rheumatic fever.

The plasma fibrinogen has been shown to be increased in rheumatic fever and in all other infections in which it has been measured. It is generally accepted that there is a close relationship between the concentration of this protein and the rate of sedimentation, and it seemed desirable to ascertain whether the plasma fibrinogen content also might be a reliable index of the rheumatic infection.

Methods. Simultaneous measurements of the corrected sedimentation index, plasma fibrinogen content and leukocyte count were made at frequent intervals on 22 patients with rheumatic fever. Eleven patients had the monocyclic, 8 the polycyclic and 3 the continuous form of the disease. The periods of observation varied from three to fourteen months. Measurements usually were made every four or five days while the patients were in the hospital and subsequently at monthly intervals. The blood specimens were collected between 9 and 11 A.M. or 2 and 4 P.M. All white blood cell counts were made by one observer, using U. S. Bureau of Standards equipment, and all counts below 9000 cells per c.mm. were considered normal. The corrected sedimentation index was obtained by the method of Rourke and Ernstene.⁶ With this method the upper limit of the normal rate is 0.35 mm. per minute. Plasma fibrinogen was measured by the method of Wu,⁷ all analyses being done in duplicate. The upper limit of the normal plasma fibrinogen content has been placed at 320 mg. per 100 cc. In 89 measurements in this laboratory on 50 normal subjects only 2 results above this level were recorded. All patients were examined for the presence of nonrheumatic infections at the time of each series of observations to exclude extraneous influences so far as possible. Salicylates were administered to all patients during the attack.

Results. *Monocyclic Type of Rheumatic Fever.* In this type of rheumatic fever the patients have severe polyarthritis, high fever and the toxic manifestations of the disease but recover without relapse. The leukocyte count drops rapidly to normal or almost normal after the institution of antirheumatic therapy, while discontinuance of the drugs frequently is followed by a slight, tem-

porary rise in the number of white blood cells.¹ The observations on patients with monocyclic rheumatic fever in the present investigation are illustrated by the following case report:

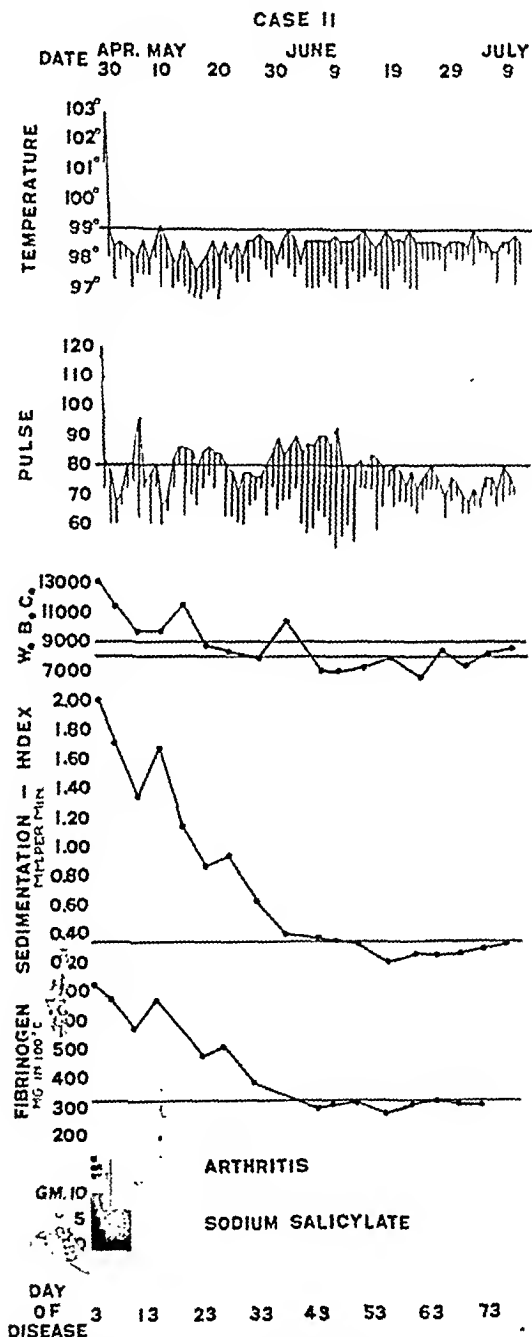


CHART 1.—Example of monocyclic type of rheumatic fever. In this and subsequent clinical charts the daily range of the temperature and pulse rate is indicated by the vertical lines in the curves for the temperature and pulse rate. Severe arthritis is represented by a heavy solid line and mild arthritis by an open dot.

Case XI (Chart 1).—T. G., a white male, aged twenty-one years, entered the hospital April 30, 1928, with severe migratory polyarthrits of two

days' duration. He had had one previous attack of rheumatic fever six years before. On admission, his temperature was 103° F. and the pulse rate 120 per minute. The heart was not enlarged. A soft systolic murmur was heard at the apex. Both ankles and the left knee were red, hot, swollen and extremely tender. The leukocyte count was 13,200 per c.mm.; the corrected sedimentation index 2 mm. per minute; and the plasma fibrinogen 721 mg. per 100 cc. All symptoms diminished rapidly with sodium salicylate therapy. On the day after admission to the hospital the temperature did not exceed 99° F., and it did not again rise above this level except on the thirteenth day of the disease. With the disappearance of symptoms, the leukocyte count, corrected sedimentation index and plasma fibrinogen content decreased rapidly, although the abrupt discontinuance of sodium salicylate at the end of the ninth day of illness was followed by a temporary intermediate rise in all three. The white blood cell count reached 8600 per c.mm. on the twenty-second day of the disease, while a normal corrected sedimentation index and plasma fibrinogen content were not recorded until the forty-fifth and forty-second days respectively.

DURATION OF SIGNS OF INFECTION IN RHEUMATIC FEVER.

Case No.	Type of rheumatic fever.	Temperature above 99° F. (days).	Pulse-rate above 80 per minute (days).	Arthritis (days).	Leukocyte count above 9000 per c.mm. (days).	Sedimentation index above 0.35 per minute (days).	Plasma fibrinogen above 320 mg. per 100 cc. (days).	Salicylates last given (day of disease).
11	Monocyclic	3	51	5	21	44	41	9
3	Monocyclic	4	4	5	24	31	35	16
20	Monocyclic	5	6	7	9	15	15	12
4	Monocyclic	6	49	30	43	61	66	18
17	Monocyclic	7	6	9	21	31	31	23
14	Monocyclic	7	23	13	26	47	52	18
15	Monocyclic	7	13	6	22	25	29	8
16	Monocyclic	8	27	6	8	14	14	18
5	Monocyclic	9	15	11	12	77	77	80
7	Monocyclic	17	34	9	18	37	51*	23
22	Monocyclic	21	8	10	26	4	54	24
1	Polycyclic	20	31	19	23	36	†	17
9	Polycyclic	26	46	28	51	.	63	42
12	Polycyclic	36	106*	38	54	29	54	58
8	Polycyclic	37	182*	37	101	82	115*	52
19	Polycyclic	55	57	68	122	122	150*	78
2	Polycyclic	76	343*	72	107	138*	†	89
21	Polycyclic	83	116	23	88	88	88	42
13	Polycyclic	85	223*	98	133	161	188*	109
18	Continuous	61	416†	57	416†	416†	416†	88
6	Continuous	75	342*	62	105	203*	182*	94
10	Continuous	192*	326†	326†	192*	36†	326†	247

* Indicates normal value first recorded at "follow-up" examination.

† Indicates result above normal value at time of last observation.

‡ Not measured.

A summary of the studies on the 11 patients with the monocyclic type of rheumatic fever is included in the table. This shows that the leukocyte count usually returned to a level below 9000 per c.mm. within a few days to two weeks after the subsidence of fever

and polyarthrititis. The corrected sedimentation index did not return to normal until the white blood cell count had been below 9000 per c.mm. for a period varying from a few days to about two months. The plasma fibrinogen usually reached a normal value at approximately the same time as the corrected sedimentation index, although in 1 of the 11 patients it remained elevated for a considerably longer time. The temperature usually became normal before the pulse rate, and at times an elevated pulse rate persisted after the leukocyte count, corrected sedimentation index and plasma fibrinogen content had become normal.

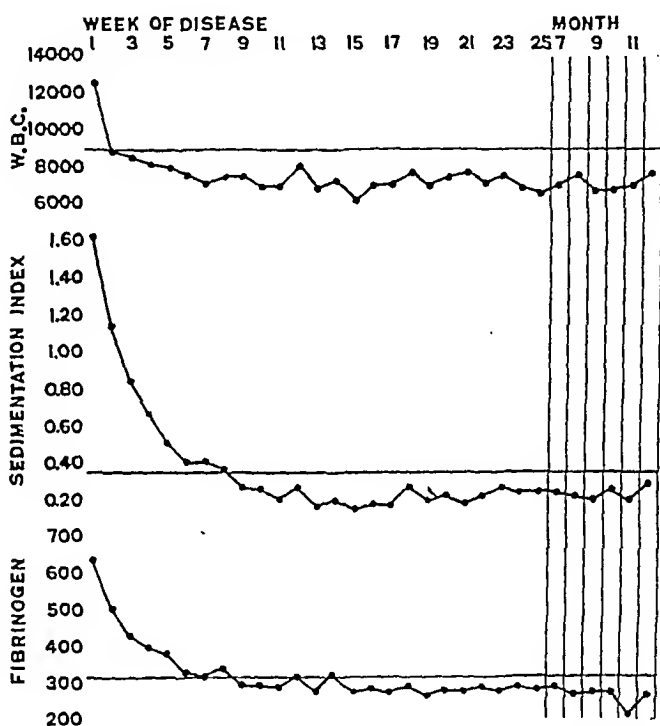


CHART 2.—Curves of the average leukocyte count, corrected sedimentation index, and plasma fibrinogen content in monocyclic rheumatic fever.

Curves of the average leukocyte count, corrected sedimentation index and plasma fibrinogen content of the patients with monocyclic rheumatic fever are given in Chart 2. During the first week of the disease there was an abrupt fall toward normal in all 3 averages, but especially in the leukocyte curve. After the fourth week of the disease the average leukocyte count was 8000 per c.mm. or less. The corrected sedimentation index and plasma fibrinogen content, however, did not become and remain normal until the ninth week of the disease.

Polycyclic Type of Rheumatic Fever. This type of rheumatic fever is characterized by the occurrence of one or more relapses of fever, tachycardia and polyarthrititis after the initial subsidence of these.

symptoms. The leukocyte count tends to remain above the normal level between relapses.¹ After the last relapse the count falls gradually to normal. The results obtained on patients with this type of rheumatic fever in the present investigation are exemplified by the following case report:

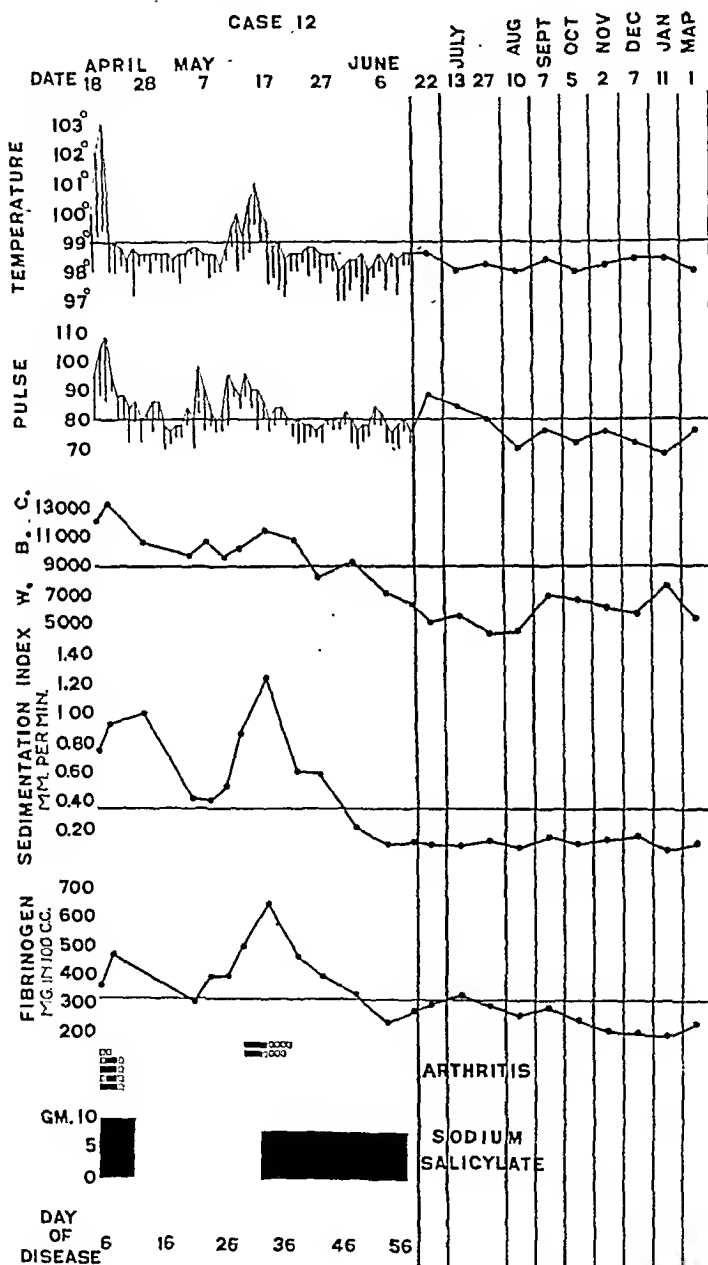


CHART 3.—Example of polycyclic type of rheumatic fever. The observations enclosed by the vertical lines on the right side of the chart were made at follow-up examinations.

CASE XII (Chart 3).—C. H., a white male, aged twenty-eight years, entered the hospital on the night of April 17, 1928, with severe polyarthrititis, high fever, and tachycardia of five days' duration. There had been no

previous attacks of rheumatic fever. The heart was not enlarged. There was a soft, blowing systolic murmur at the apex. The right knee and right ankle were swollen, red, hot and extremely tender. The left knee, left ankle and right wrist were similarly but less severely involved. Salicylate therapy was instituted immediately. On the following day the leukocyte count was 12,100 per c.mm., the corrected sedimentation index 0.75 mm. per minute, and the plasma fibrinogen content 375 mg. per 100 cc. In spite of antirheumatic therapy, the temperature and pulse rate reached new peaks on both the second and third days after admission, and the arthritis continued. This was attended by an increase in the leukocyte count, corrected sedimentation index, and plasma fibrinogen content. On the fourth day, the temperature did not exceed 98.8° F., and after this the other symptoms subsided rapidly. A slight rise in the corrected sedimentation index was observed after the abrupt discontinuance of sodium salicylate at the end of the sixth day in the hospital, but the white blood cell count was not similarly affected. Except for the plasma fibrinogen measurement on the twenty-second day, the leukocyte count, corrected sedimentation index and plasma fibrinogen content remained above normal levels after the initial subsidence of symptoms. In the fifth week of illness the patient again developed fever, rapid pulse, and polyarthritis, accompanied by a decided increase in the leukocyte count, corrected sedimentation index, and plasma fibrinogen content. After salicylate therapy had been reinstituted, the symptoms promptly subsided. The leukocyte count and plasma fibrinogen content reached a normal level on the fifty-fifth day of illness, and the corrected sedimentation index became normal on the fiftieth. The subsequent course was uneventful, and the patient was discharged on the sixtieth day after the onset of symptoms.

A summary of the studies on the 8 patients with the polycyclic type of rheumatic fever is included in the table. In general, the leukocyte count tended to remain elevated for a longer time after the final subsidence of fever and polyarthritis than in the monocyclic form. In 4 of the 8 patients the corrected sedimentation index and white blood cell count reached normal levels almost simultaneously, while in 3 others the sedimentation index remained elevated for three or four weeks after the leukocytes had dropped below 9000 per c.mm. The plasma fibrinogen content usually reached a normal level either at the same time as the corrected sedimentation index or within the following four weeks. The pulse rate tended to remain elevated longer than the corrected sedimentation index and plasma fibrinogen content.

Curves of the average leukocyte count, corrected sedimentation index and plasma fibrinogen content in the patients with polycyclic rheumatic fever are given in Chart 4. The leukocyte curve drops steadily during the first five weeks of the disease. It then runs an irregular, wavelike course, and does not remain below the upper limit of normal until after the fourteenth week. The curves of the average corrected sedimentation index and plasma fibrinogen content roughly parallel that of the average leukocyte count but do not remain within normal limits until after the twenty-second week.

Continuous Type of Rheumatic Fever. In this form of the disease tachycardia and intermittent elevations of temperature persist for

a long period, and cardiac involvement is an outstanding feature. Recurring attacks of polyarthrititis, although common, are a less prominent part of the clinical picture. In children subcutaneous nodules frequently are present. The white blood cell count is not appreciably affected by antirheumatic therapy and remains elevated as long as the infection continues active.¹ The results obtained on patients with this type of the disease in the present study are illustrated by the following example:

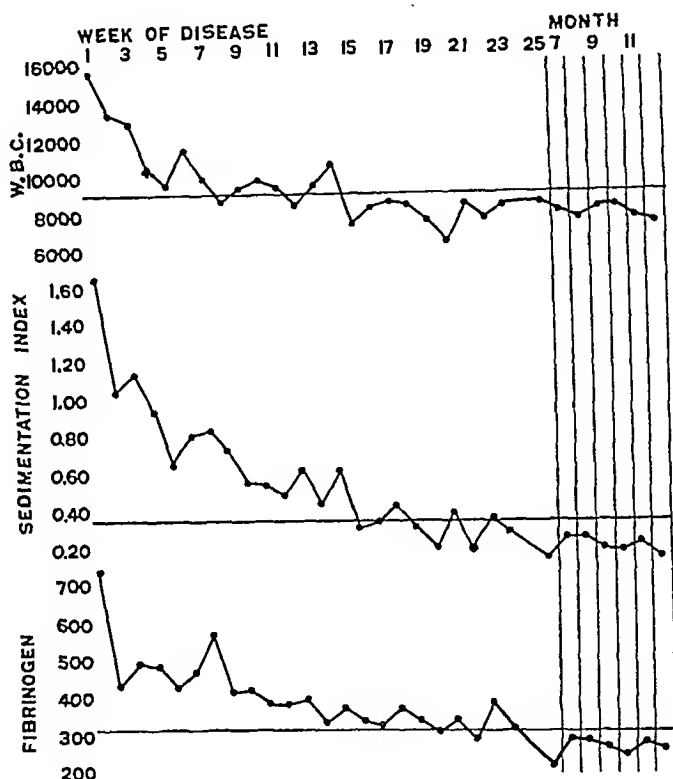


CHART 4.—Curves of the average leukocyte count, corrected sedimentation index, and plasma fibrinogen content in polycyclic rheumatic fever.

CASE VI (Chart 5).—M. C., a white male, aged twenty-two years, was admitted to the hospital April 30, 1928, with polyarthrititis, fever and tachycardia of three days' duration. He had had one earlier attack of rheumatic fever sixteen months before. The heart was slightly enlarged. A presystolic and harsh systolic murmur replacing the first sound were heard at the mitral area. At the base the pulmonic second sound was decidedly accentuated. The *P-R* interval of the electrocardiogram was 0.22 seconds. Both ankles were red, moderately swollen, warm, and very tender. The left knee was slightly swollen and moderately tender. The initial leukocyte count was 14,100 per c.mm., and the first sedimentation index and plasma fibrinogen values were distinctly elevated. The patient remained in the hospital for three and a half months, during which time there were several temporary slight elevations of temperature. The tachycardia persisted and at irregular intervals became much more pronounced; this rapid pulse-rate, in fact, constituted the principle symptom of the infection. Three courses of sodium salicylate were given. The leukocyte curve followed a

wavelike course and did not fall below 9000 per c.mm. until the one hundred and sixth day of illness. The curve of the sedimentation index followed a more distinctly downward course in the first half of the period of hospitalization; but in the ninth week of the disease it increased markedly and did

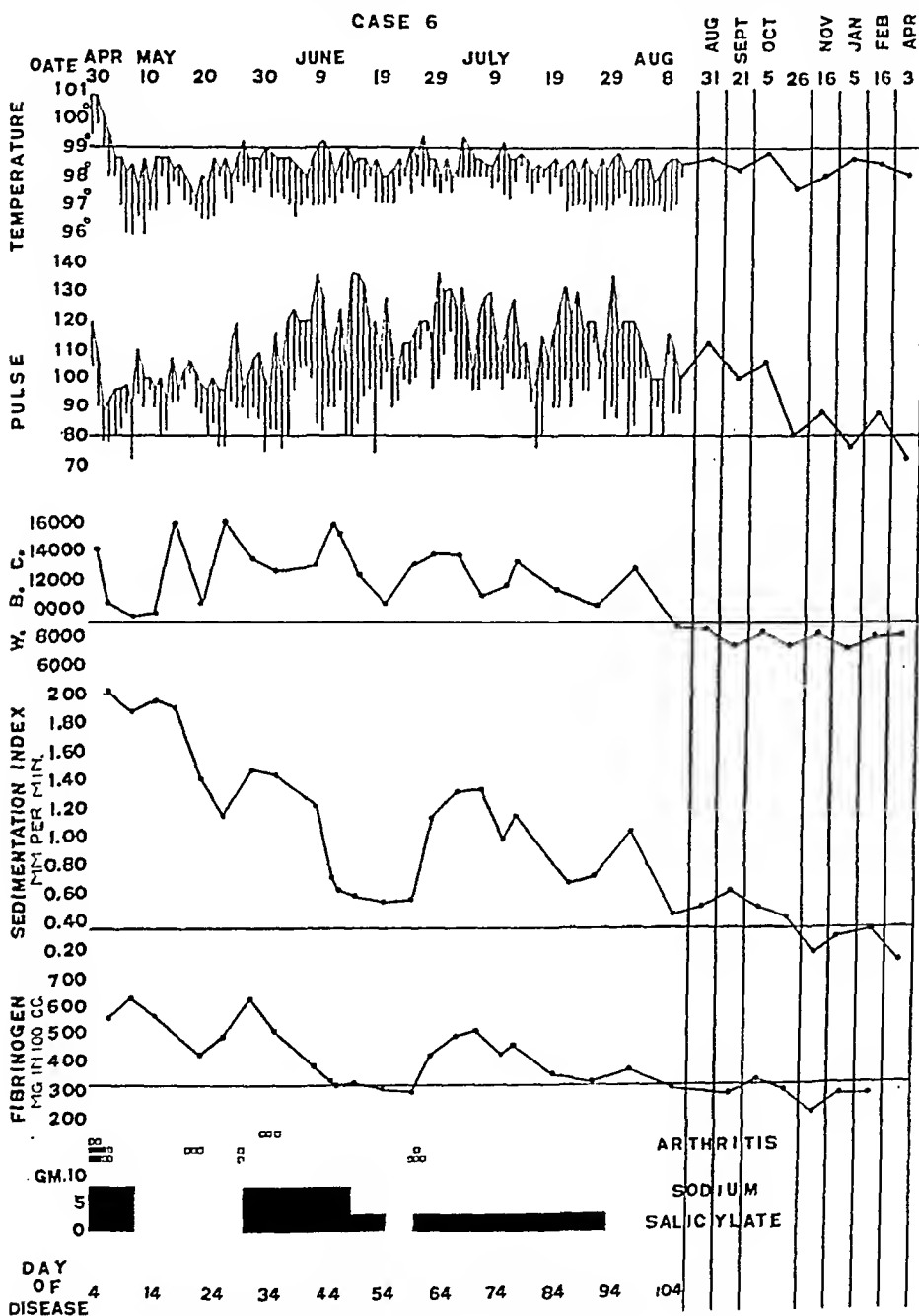


CHART 5.—Example of continuous type of rheumatic fever.

not become normal until the leukocyte count had been below 9000 per c.mm. for three months. The plasma fibrinogen curve roughly paralleled that of the sedimentation index, although it reached a normal level a few weeks earlier than the latter.

A summary of the studies on the 3 patients with the continuous type of rheumatic fever is included in the table. In 1 patient the pulse rate, corrected sedimentation index, plasma fibrinogen content and leukocyte count were still above normal fourteen months after the onset of the illness. In another the plasma fibrinogen remained elevated for two and a half months and the sedimentation index for over three months after the leukocyte count had become normal. In the third the pulse rate, sedimentation index and plasma fibrinogen were still elevated after the white blood cell count had been below 9000 per c.mm. for over four months.

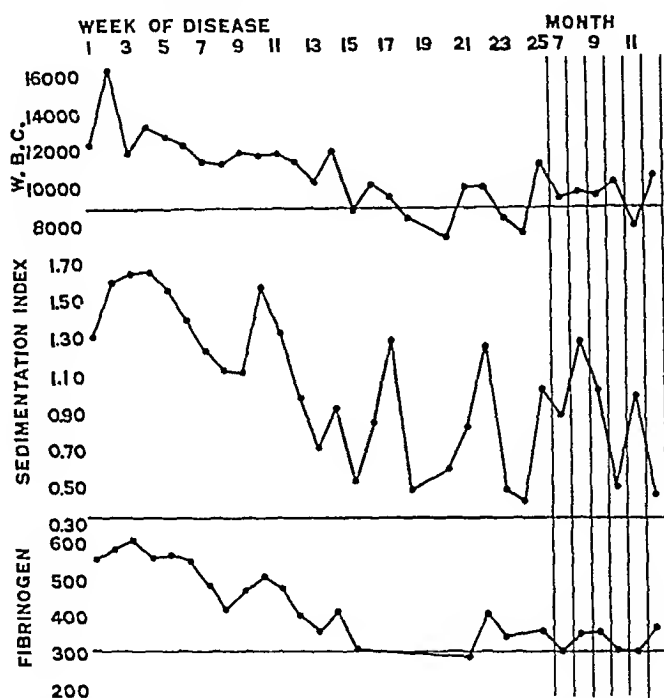


CHART 6.—Curves of the average leukocyte count, corrected sedimentation index, and plasma fibrinogen content in the continuous form of rheumatic fever.

Curves of the average white blood cell count, corrected sedimentation index and plasma fibrinogen content in the patients with the continuous type of rheumatic fever are presented in Chart 6. The small number of cases studied introduces a large error in these averages. Each curve, however, follows an irregular, gradually downward course, and in the twelfth month of the disease none had yet reached a normal level.

Discussion. The results of the present investigation indicate that the corrected sedimentation index is a more sensitive criterion of activity of the infection in rheumatic fever than the leukocyte count. In all types of the disease the sedimentation rate, with few exceptions, remained elevated for several days to a few weeks after the white blood cell count had become normal. Had there been a

constant interval between the times when the two measurements reached normal it might have been assumed that the persistent elevation of the sedimentation rate was only a residual manifestation of a preceding systemic reaction. The fact that this period was variable, however, indicates with great probability that such was not the case and that the elevation of the corrected sedimentation index was due to persistent low-grade rheumatic infection. It is a widely accepted rule that no patient with rheumatic fever should be allowed out of bed until he has been free of all symptoms and signs of the infection for two or three weeks, during which time he should not have been receiving antirheumatic drugs. Leukocytosis is usually the last of the signs of infection, heretofore employed, to disappear. The fact that in a majority of the patients in the present series, the corrected sedimentation index returned to normal within three weeks of the time when the first normal leukocyte count was recorded (see table), lends general support to the above clinical formula. On the other hand, the instances in which the corrected sedimentation index remained elevated for more than three weeks after the first normal white blood cell count, indicate the advisability of substituting the sedimentation test for the leukocyte count in deciding when the infection has ceased to be active. The rheumatic infection cannot be considered arrested until the corrected sedimentation index has returned to and remained normal, and it is believed that no patient should be allowed out of bed until this time.

The corrected sedimentation index showed a greater relative increase above normal at the height of the illness than did the leukocyte count. In the monocyclic type of the disease the average leukocyte count in the first week of illness was 60 per cent above normal, while the average sedimentation index was increased 360 per cent. In the polycyclic type the average leukocyte count in the first week of the disease was 85 per cent above normal, while the corrected sedimentation index was increased 370 per cent. In the continuous type the maximum average leukocyte count was 94 per cent above normal, while the corresponding average of the corrected sedimentation index was 360 per cent above normal. Exacerbations of the infection in the polycyclic and continuous types of the disease were preceded or accompanied by distinct increases in both the leukocyte count and corrected sedimentation index, but the rise in the sedimentation index usually was of much greater relative extent than the increase in the number of white blood cells. These observations suggest that the corrected sedimentation index is a more sensitive indicator of the infection than the leukocyte count.

There was evidence that both the leukocyte count and the corrected sedimentation index were depressed by antirheumatic drugs; but, in general, the sedimentation index seemed to be less affected in this way than the white blood cell count. The subsidence of

symptoms under salicylate therapy usually was accompanied by a pronounced drop toward normal in both measurements. In the monocyclic type of the infection the leukocyte count occasionally reached a normal level at this time, but in no instance was such a profound depression of the corrected sedimentation index observed. In patients with the polycyclic or continuous type of the disease the leukocyte count and corrected sedimentation index remained above normal between exacerbations of the infection, even though salicylate therapy was continued without interruption. In all types of the disease a slight increase in the white blood cell count and corrected sedimentation index followed by a prompt return to the previous level frequently was observed after discontinuance of salicylates. Occasionally, however, an increase was recorded in only one of these factors.

A general parallelism was observed throughout between the plasma fibrinogen content and the corrected sedimentation index. Since these two measurements yield almost identical information, both of them need not be made routinely for any practical advantage. The sedimentation test is much simpler than any available method for measuring plasma fibrinogen and is, therefore, the measurement of choice. It should be performed at regular intervals on all patients with rheumatic fever. If this is not possible, measurements should be made every four or five days after the leukocyte count has dropped below 9000 per c.mm. until a repeatedly normal corrected sedimentation index is recorded. The patient may then begin to be out of bed for a part of each day.

Summary. 1. The corrected sedimentation index, plasma fibrinogen content, and leukocyte count were measured at frequent intervals in 22 patients with rheumatic fever.

2. At the height of the illness the corrected sedimentation index showed a greater relative increase above normal than did the leukocyte count.

3. Both the leukocyte count and the corrected sedimentation index were depressed somewhat by salicylates, but, in general, the sedimentation index seemed to be less affected than the white blood cell count.

4. A slight increase in the leukocyte count and corrected sedimentation index followed by a prompt return to the previous level was observed frequently after discontinuance of salicylates.

5. With exacerbations of the infection in the polycyclic and continuous types of the disease, there was usually a greater relative increase in the corrected sedimentation index than in the leukocyte count.

6. In all types of the disease the corrected sedimentation index, with few exceptions, remained elevated for several days to a few weeks after the leukocyte count had become normal.

7. A general parallelism was observed throughout the course of

the disease between the plasma fibrinogen content and the corrected sedimentation index.

8. The observations indicate that the corrected sedimentation index and plasma fibrinogen content furnish almost identical information and are more accurate indices of the infection in rheumatic fever than the leukocyte count. The corrected sedimentation index is the preferable clinical test on account of its greater simplicity. The infection cannot be considered arrested until the corrected sedimentation index has become and remained normal.

REFERENCES.

1. Swift, H. F., Miller, C. P. Jr., and Boots, R. H.: The Leukocyte Curve as an Index of the Infection in Rheumatic Fever, *J. Clin. Invest.*, 1924, 1, 197.
2. Herrmann, H.: Die Blutkörperchensenkungsgeschwindigkeit bei Arthritiden und Rheumatischen Affektionen der Muskulatur, München. med. Wehnschr., 1924, 71, 1714.
3. Kahlmeter, G.: Ueber die Bedeutung der Fähreussehen Senkungsreaktion bei akuten und chronischen Arthritiden, *Klin. Wehnschr.*, 1926, 5, 889.
4. Sharpless, F. C.: Blood Sedimentation Time in Acute Rheumatic Fever, *Atlantic Med. J.*, 1927, 31, 10.
5. Rourke, M. D., and Plass, E. D.: An Investigation of Various Factors Which Affect the Sedimentation Rate of the Red Blood Cells, *J. Clin. Invest.*, 1929, 7, 365.
6. Rourke, M. D., and Ernstene, A. C.: A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in Cell Volume Percentage of the Blood, *J. Clin. Invest.* (In press.)
7. Wu, H.: A New Colorimetric Method for the Determination of Plasma Proteins, *J. Biol. Chem.*, 1922, 51, 33.

THE VALUE OF BLOOD BILIRUBIN ESTIMATIONS IN THE DIFFERENTIAL DIAGNOSIS OF CEREBROVASCULAR ACCIDENTS.

BY GARNETT CHENEY, M.D.

ASSISTANT VISITING PHYSICIAN ON THE STANFORD MEDICAL SCHOOL SERVICE AT THE SAN FRANCISCO COUNTY HOSPITAL AND LAGUNA HONDA HOME.

A PARESIS or paralysis of any part of the body, most often a hemiplegia, more or less sudden in onset, and dependent on a disturbed circulation, may be classed as a cerebrovascular accident. The condition is commonly described as "a stroke," or apoplexy, where apoplexy is used in its original meaning of being struck down, rather than being confined to hemorrhagic conditions. Pathologically such an accident is due to thrombosis of a bloodvessel, a hemorrhage, or an embolus lodged within the vessel. Cerebrovascular spasm or a slowing of the blood stream due to a fall in blood pressure might also be included. The clinical picture has been well recognized since the time of Charcot, and little has developed since that time to distinguish the kind of process producing the paralysis. One is struck by the lack of uniform opinion

as to the relative incidence of such common lesions and by the clinician's inability in the majority of cases to make an accurate diagnosis. Certain findings have been described which may be taken as the basis for a reasonably certain diagnosis, but after assembling all the data available it is often impossible to come to a decided conclusion. As the treatment of a case of cerebral thrombosis may be diametrically opposed to the treatment of a case of hemorrhage, any diagnostic procedure which may assist in distinguishing the nature of the lesion would be of great value. In 1928 Wilder¹ showed that studies of the blood serum bilirubin content might be relied upon to give the correct diagnosis in most cases.

Blood Bilirubin Tests. There are two outstanding methods for determining blood serum bilirubin content: The icteric index and the Van den Bergh reactions. The technique of both is described in most books on clinical pathology. The first is a simple quantitative measurement by an arbitrary standard. Average normal values range between 3 and 7 units. The second is both a quantitative and qualitative test. The first part of the test is called the immediate direct reaction. It is only positive when the source of the bilirubin increase is in the liver and biliary tract, and is always negative when the pigment increase is hematogenous in origin. The second part of the test is a quantitative measure of the pigment by degree of dilution. It is recorded in both units and in milligrams per 100 cc. of blood. Normal figures are 0.2 to 0.4 units or 0.5 to 2 mg.

Originally the two reactions were thought to depend on a difference between the bilirubin formed from bile pigment and that formed from blood pigment which would distinguish the source of a disordered pigment metabolism. Blankenhorn² and others now feel that the difference in the reactions is due to the rate of absorption of the pigment into the blood stream. When it is absorbed slowly, as is usual in hematogenous icterus, it is combined with protein and gives only the indirect reaction. When it enters the blood stream rapidly, as in obstructive icterus, no such combination takes place and the direct reaction occurs. Combined and uncombined bilirubin in excess may both be present, giving the so-called delayed direct and biphasic reactions. The interpretation of these is difficult clinically and has given rise to considerable criticism of the original claims for the test.

As quantitative tests, both the icterus index and the Van den Bergh tests are reliable in measuring the degree of jaundice barring technical errors, and represent one of the recent really important advances in clinical pathology. Qualitatively, if the direct Van den Bergh reaction is negative an increase in blood bilirubin is considered as very probably hematogenous in origin, and if the direct reaction is positive there is some disturbance in bile pigment

metabolism. In clear-cut reactions then the Van den Bergh test can be used to demonstrate a hematogenous cause for an increase in blood serum pigment.

Relation of Bilirubin Tests to Apoplexy. The application of these tests to the differential diagnosis of cerebrovascular accidents has already been attempted by Wilder¹ in Vienna. In a cerebral hemorrhage the extravasated blood is in an enclosed space, and the blood pigment will be gradually absorbed from the affected area and transported by the blood stream elsewhere. As this does not occur to any degree in cerebral softening, evidence of the absorbed pigment in the blood serum might serve to distinguish the two types of brain lesions one from the other. There are three questions of prime importance to be considered: (1) Are all cerebral hemorrhages large enough to give definite symptoms, sufficiently large to cause an increase in serum bilirubin content? (2) In large areas of so-called red softening is there sufficient blood extravasated to affect the normal icteric index? (3) If a cerebral hemorrhage constantly raises the icteric index does it do so early enough to be of any practical clinical value? Only a careful study of a large series of cases can answer these questions.

Wilder's report on the subject is the only one which has appeared in the available literature to date, and it seems strange that a problem which may offer so much has been so neglected. This author presented two groups of cases of cerebral hemorrhage. One was confirmed by postmortem examination, and in the other the clinical diagnosis was practically certain. Blood bilirubin was measured by dilution ratios, and the icteric index and qualitative Van den Bergh reactions were not reported. In the first group there were 8 cases tested within six days after the accident. All but one showed a clear-cut increase in serum bilirubin. The exception was only a cherry-sized hemorrhage tested one day after onset, and it had broken into the ventricle. Two of the cases showed the increase one day after the insult. In the second group there were 5 cases which included a meningeal hemorrhage, an abscess hematoma, two brain tumors and a case with obscure test findings. The first 4 showed a marked increase in blood bilirubin, 2 after the first day. However, one test showed the increase after twenty-seven days. Two other hemorrhage cases showed normal values after thirty-five days and sixty days. Five out of 6 cases with normal serum dilution values showed softening at autopsy, the sixth had icterus and gall stones. In 25 other cases thought to be softening, all but 3 gave normal values, the exceptions were not proven not to have bled. Tests on 8 other cases of miscellaneous nonhemorrhagic cerebral disorders showed no tendency toward icterus.

Wilder concluded that one could determine with a very great probability whether an apoplectic insult was due to hemorrhage or not. The bilirubin is increased within the first twenty-four hours

and may remain up for four weeks. Consequently the test is extremely important in differential diagnosis. The author was handicapped in some of his cases by not being able to distinguish between icterus of hepatogenous and hematogenous origin.

Present Series. In the 50 cases of cerebrovascular accident which compose the present series the blood bilirubin was estimated from one day to three months after the ictus. Of this number 11 died, but autopsies were obtained on only 5 cases. Although there is a postmortem confirmation of the diagnosis in so few instances, the results of the bilirubin tests seem to bear important relationships to the clinical findings. The cases have been divided up into groups according to whether they showed positive, negative or doubtful tests. As with many laboratory tests, it is difficult to establish a clear-cut division between normal and abnormal readings. The normal range of the icterus index values has been taken as from 4 to 7 units inclusive. A reading of 8 units, although often accepted as a definite increase, has been regarded as a borderline reading. The normal quantitative Van den Bergh readings are 0.2 to 0.4 units; anything over 0.4 is judged an increase. Twenty cases showed an increase in serum pigment. Three of these were discarded as the direct Van den Bergh was positive, indicating a biliary tract pigment metabolism disturbance, which would obscure any changes due to hematogenous causes. Ten cases gave normal bilirubin values, and 5 more were in the borderline group. In the remaining 15 cases there was insufficient data to warrant their inclusion.

In the 17 cases with a clear-cut increase in the icterus index and a negative direct Van den Bergh reaction there is considerable lack of correlation between the clinical findings and those of the tests. (Table I.) Although the clinical diagnosis was frequently in doubt, an impression was usually expressed, based upon the symptomatology and findings. All types of onset occurred and many of the patients were not comatose. Some had had previous attacks. Although the blood bilirubin tests would indicate that all suffered from cerebral hemorrhage, the following clinical impressions were recorded in the 17 histories. Six were thought to have hemorrhage, 8 thrombosis (including 3 syphilitics), 1 trauma and 2 uremia. Only 5 of these 17 cases died while in the hospital. One, the trauma case, showed at autopsy, a fractured skull, which had been undiagnosed by Roentgen ray, and a large subdural hemorrhage. Of the remaining 4 deaths, 2 came to autopsy and in both the clinical diagnosis of uremia was confirmed. Both showed multiple small brain hemorrhages. In the other 2 cases 1 was thought to be hemorrhage, the other thrombosis. Thus, 9 of the 17 showed some evidence of hemorrhage.

Controversial findings also exist in those cases with normal serum bilirubin values but to a lesser degree. The tests should indicate

that no hemorrhage has occurred. The clinical impressions in this group of 10 cases (Table II) were: hemorrhage, 2; thrombosis, 7 (including 1 case of syphilis and 1 case of probable cerebral embolus); trauma, 1. Three of these patients died, including the one suspected of embolus, but no autopsies were held. There were 2 cases of thrombosis in the original series which came to anatomical examination, both of whom had positive direct Van den Bergh tests. Such findings emphasize the importance of the qualitative Van den Bergh findings in these tests.

TABLE I.—CASES OF CEREBROVASCULAR ACCIDENT WITH INCREASED BLOOD BILIRUBIN.

Case No.	Interval before tests.	Icterus index.	Van den Bergh reaction.		Clinical impression.	Remarks.
			Direct.	Indirect.		
3	3 mos.	11.5	Neg.	0.50	Hemiplegia; thrombosis	Died; urinary tract infection.
4	2 "	13.4	Neg.	0.70	Paresis with hemiplegia	Malaria; fair recovery.
5	7 days	14.0	Neg.	0.60	Hemiplegia; thrombosis	Spastic paralysis.
8	4 "	14.0	Neg.	0.50	Hemiplegia; thrombosis	Attacks of syncope.
9	10 "	11.0	Neg.	...	Hemiplegia thrombosis	Hypertension; one previous "stroke."
10	5 "	12.0	Neg.	0.80	Uremia with hemiparesis	Autopsy: multiple small cerebral hemorrhages.
14	5 "	12.0	Neg.	0.80	Cerebrovascular syphilis with hemiplegia	Previous attack.
19	6 "	9.2	Hemiplegia hemorrhage	Died.
31	7 "	15.0	Skull fracture	Autopsy: skull fracture (not seen in Roentgen ray) and large subdural hemorrhage.
32	"Sometime ago"	14.0	Neg.	0.85	Hemiplegia thrombosis	Had five "strokes."
34	2 mos.	15.8	Neg.	0.7	Hemiplegia; hemorrhage	Hypertension; good recovery.
37	7 days	12.0	Cerebrovascular syphilis with hemiplegia	
42	1 mo.	9.0	Neg.	...	Hemorrhage	Hypertension; fair recovery.
43	2 days	12.0	Neg.	...	Uremia with convulsive seizures	Autopsy: glomerular nephritis; multiple small brain hemorrhages.
45	8 "	10.0	Hemorrhage	
46	14 "	13.0	Hemorrhage	
48	3 "	27.0	Hemorrhage	

In the 5 cases with borderline bilirubin values (Table III) only 2 had Van den Bergh reactions done on them. The blood was tested on all of them between seven and twenty-six days after the

ictus. Three were thought to be thrombosis, and these cases might represent the so-called "red softening" where some hemorrhage has taken place into the infarcted area. One case was diagnosed encephalitis, and one case simply cerebrovascular accident. One case thought to be thrombosis died, but there was no autopsy.

TABLE II.—CASES OF CEREBROVASCULAR ACCIDENT WITH NORMAL BLOOD BILIRUBIN.

Case No.	Interval before tests.	Icterus index.	Van den Bergh reaction.		Clinical impression.	Remarks.
			Direct.	Indirect.		
6	36 hrs.	7.0	Neg.	0.3	Hemorrhage	Died; extreme hypertension.
17	7 days	7.5	Neg.	0.2	Hemiplegia; embolus	Died; had quinidin.
22	3 mos.	7.5	...	0.3	Hemiplegia; cerebrovascular syphilis	Malaria; fair recovery.
23	5 days	6.0	Hemiparesis; hemorrhage	Died; bronchopneumonia.
27	2 mos.	7.3	Hemiplegia; thrombosis	Previous attack.
28	1 mo.	4.2	Hemiplegia; thrombosis	Hypertension.
36	3 days	6.0	Hemiplegia; thrombosis	Three previous "strokes."
40	13 "	6.0	Neg.	...	Hemiplegia; thrombosis.	
44	1 mo.	6.0	Neg.	...	Monoplegia; thrombosis	Good recovery.
50	7 days	6.0	Neg.	...	Head trauma	Good recovery.

TABLE III.—CASES OF CEREBROVASCULAR ACCIDENT WITH INDEFINITE INCREASE IN BLOOD BILIRUBIN.

Case No.	Interval before tests.	Icterus Index.	Van den Bergh reaction.		Clinical impression.	Remarks.
			Direct.	Indirect.		
15	7 days	8.0	Hemiparesis; thrombosis.	
16	10 "	8.0	Neg.	...	Hemiplegia; thrombosis	Died of subsequent "stroke."
20	10 "	8.3	Neg.	0.4	Cerebrovascular accident	Good recovery.
26	26 "	8.7	Neg.	0.5	Hemiplegia; thrombosis	Previous attack.
49	14 "	8.0	Epidemic encephalitis	Good recovery.

Eight cases of the 35 had positive blood Wassermanns and other evidence of syphilis. Most textbooks state that hemiplegias in syphilis are due to thrombosis. As this type of cerebrovascular

accident responds to antiluetic therapy, as a rule, anatomic examinations are rarely possible. Ophüls³ records 2 in which hemorrhages were found. This question of the exact nature of the lesion in luetic paralyses is a very important one as the tests would indicate that it is a hemorrhage, despite all the clinical impressions to the contrary. In 6 of the 8 cases the icterus index ranged between 11 and 14 units, although 1 of these showed a delayed direct Van den Bergh reaction three months after the accident. The tests were made on the other 5, five to ten days after onset, except in a case of paresis which showed a positive test after eight weeks. The 2 cases which did not show a definite increase in serum pigment were both only weakly positive in their Wassermann reactions. One of these was in an old man with marked arteriosclerosis and hypertension, and in the other the test was made three months after the onset of the paralysis.

In most instances the blood pigment tests were made within two weeks after the onset of the cerebral accident, but this was not always possible, and in 7 cases the time interval was from one to three months. As far as our present knowledge goes probably no conclusions can be drawn from normal values obtained after the first four weeks. However, four positive readings were obtained in these 7 cases, and should be indicative of hemorrhage with as yet incomplete absorption of pigment from the old blood clot.

It is also interesting to note that in this series of cases there was no constant relationship between blood pressure readings and the type of lesion indicated. Many cases of high blood pressure clinically and serologically seemed to be thrombosis, while several cases with low blood pressure were evidently hemorrhage. Both types of blood pressure were encountered after the cerebrovascular accident.

Conclusion. On the basis of Wilder's work and the cases herein reported, it seems justifiable to conclude that a definite increase in the icteric index with a negative direct Van den Bergh reaction following a cerebrovascular accident usually indicates that a hemorrhage has occurred, and that a normal index after the first day, but within the first few weeks, is strong evidence against a hemorrhage. If these conclusions are borne out by other workers in larger series of cases where autopsies are obtained estimations of serum bilirubin will present a most important basis for the differential diagnosis of the lesions.

REFERENCES.

1. Wilder, J.: *Wien. klin. Wchnschr.*, 1927, 40, 1158.
2. Blankenhorn, M. A.: *Ann. Int. Med.*, 1927, 1, 74.
3. Ophüls, W.: *A Statistical Survey of Three Thousand Autopsies*, 1926, p. 261

THE PROGNOSTIC VALUE OF THE INITIAL LEUKOCYTE AND DIFFERENTIAL COUNT IN LOBAR PNEUMONIA.

BY RICHARD MIDDLETON, M.D.,

AND

JOHN H. GIBBON, JR., M.D.

(From the Medical Service of the Pennsylvania Hospital.)

ALTHOUGH clinical methods of examination of the blood are fairly well standardized, there is still no lack of interest in efforts to devise means of obtaining additional diagnostic and prognostic information from the procedure. The stained blood smear has offered a fertile field for careful investigation, and numerous methods of getting prognostic data from the differential leukocyte count have been introduced. Most of these, while admittedly based on sound premises, have the disadvantage of being complex or costly in time and have not been widely adopted. A determination of the complete Arneth index, to cite the most widely known example, requires forty-five minutes of an expert worker's¹ time and even the modified simpler form of Arneth count which has been used more recently consumes twenty minutes and calls for practiced nicety of judgment in distinguishing small variations in shape and number of segments among the nuclei of the leukocytes.

Weiss¹ and Reznikoff² have described Schilling's valuable simplified method of gauging the severity of infectious toxic states. It consists essentially in subdividing the polymorphonuclear leukocytes into two groups—young and adult, or unsegmented and segmented—and determining the percentage of each. They lay much less stress, however, on the individual count than on the trend of a series of counts taken at fairly short intervals. A high and increasing percentage of immature polymorphonuclear leukocytes indicates a grave illness, while a low or diminishing number foreshadows recovery.

Hinkleman³ has pointed out the prognostic value of the determination of the absolute number of the various types of leukocytes per cubic millimeter of blood. He has formulated the following surgical prognostic rules: "(1) So long as all the cells commonly represented in the white count are present in normal absolute numbers, the patient's condition is good and the prognosis can be counted favorable. . . . (3) When the small lymphocytes begin to fall below normal absolute numbers, this marks the real beginning of disorganization of Nature's fighting force and the point at which the case should always receive a serious consideration. There is still a chance of recovery, depending on how quickly and thoroughly the cause can be removed." Todd and Sanford⁴ give

the normal range of polymorphonuclear leukocytes as 3000 to 7000 per c.mm. and of lymphocytes, 1200 to 3000 per c.mm.

Suppression of the absolute number of lymphocytes usually carries with it as a correlative an undue increase in the percentage of other forms, chiefly polymorphonuclears. Since Sondern's⁵ contribution, an increase in the polymorphonuclear leukocyte percentage out of proportion to the increase in total count has been repeatedly recognized as indicative of severe infection or low resistance. Gibson⁶ devised a useful chart to portray by the slant of a line the proportion or disproportion between total increase and polymorphonuclear increase. A glance at such a chart gives a good idea of the danger one's patient is in. The inconvenience of dependence on a chart has caused Walker⁷ to construct a simple formula which gives the same information in the form of a numeral which he has designated the "Index of Resistance." Walker's formula is as follows:

$$IR = (T-10) - (P-70).$$

In this formula IR is the index of resistance, T, the total leukocyte count expressed in thousands, and P, the polymorphonuclear leukocyte percentage. Disproportionately rapid rise in the percentage of polymorphonuclear leukocytes results in a negative value when this formula is applied. It is to be noted that Walker's formula reveals his choice of 70 per cent as the upper limit for polymorphonuclears in the normal differential count, in contrast to Gibson's original figure of 75 per cent.

Owing to the rush of work in the ordinary general hospital, it is evident that any laboratory method of prognosing the outcome of acute infectious diseases which depends on observing the trend of a series of differential counts taken at short intervals is not likely to find wide adoption. The average patient will probably receive little more than an initial complete count including smear for diagnostic purposes, supplemented by such leukocyte counts as seem called for by the progress of the disease. For this reason, we have recently interested ourselves in the question of the prognostic significance of the admission blood counts taken by interns at the Pennsylvania Hospital on patients admitted to the medical services of Dr. George W. Norris and Dr. Thomas McCrae. Lobar pneumonia was selected as the disease par excellence for this purpose because of its acuteness, severity, ease of clinical recognition and nonspecific blood picture, which apparently may serve as a type for a large number of acute infectious processes.

Does a single, frequently very early, complete blood count enable one to tell how "hard hit" a patient is with pneumonia and to estimate the outcome with any degree of accuracy? In an attempt to answer this question we have reviewed the records of 100 patients who recovered from lobar pneumonia and 60 who died of the disease. There was no selection of cases except that only frank lobar pneu-

monia was accepted. A large majority of the patients were adults, this being a general hospital with no pediatric beds.

In Table I we have tabulated side by side the total leukocytic response to the disease of the two groups of patients. Accepting 5000 to 10,000 as the normal range of leukocytes, it will be seen that among the patients who recovered there was not a single leukopenia, whereas among the fatal cases 10 per cent exhibited leukopenia. Nine per cent of those who recovered and 30 per cent of those who died had no leukocytosis. Forty-seven per cent of the patients who recovered had leukocyte counts above 20,000; only 16 per cent of the fatal cases had counts this high. These figures decisively con-

TABLE I.—TOTAL LEUKOCYTIC RESPONSE OF 100 NON-FATAL AND 60 FATAL CASES OF LOBAR PNEUMONIA.

Leukocyte count.	Recovered.		Died.	
	Number.	Per cent.	Number.	Per cent.
Below 5,000	0	0	6	10
5,000 to 10,000	9	9	12	20
10,000 to 15,000	15	15	16	27
15,000 to 20,000	29	29	16	27
20,000 to 30,000	33	33	8	13
Above 30,000	14	14	2	3
Total	100	100	60	100

firm the ominous significance of leukopenia in pneumonia and the favorable portent of high leukocytosis. The average leukocyte count of those who recovered was 21,046, and of those who died, 14,700.

The average absolute number of polymorphonuclear leukocytes per cubic millimeter among the patients who recovered as 18,130 and of lymphocytes 2159, as compared with an average of 12,711 polymorphonuclears and 1437 lymphocytes among those who died. Nineteen per cent of the patients who recovered and 52 per cent of those who died had absolute lymphocyte counts of less than 1200 per c.mm. Thus it would appear that a lymphocyte count below the low normal absolute number is often of grave significance, while a normal or higher count is not accompanied by a corresponding assurance of favorable termination of the disease.

The index of resistance was calculated according to Walker's formula. Table II portrays the result. Among the patients who recovered, 32 per cent had indexes which were positive or zero, the rest being minus quantities. The lowest index was -20, shared by 3 patients, all of whom convalesced without incident. The highest index of resistance was +29. This patient also had the highest leukocytosis in the series (55,100). He developed empyema and recovered after thoracotomy. Incidentally, his Wassermann reaction was strongly positive.

Among the fatal cases, only 15 per cent had indexes which were positive or zero, the rest being negative. The lowest index in the

group was -31 . This patient had a leukocyte count of 5200, with 96 per cent of polymorphonuclears. He died on the ninth day of the disease. All of the 10 patients whose initial index of resistance was below -20 are counted among the fatal group.

TABLE II.—ANALYSIS OF INDEXES OF RESISTANCE OF 100 NON-FATAL AND 60 FATAL CASES OF LOBAR PNEUMONIA.

Index of resistance.	Recovered.		Died.		Total cases.	Recovered, per cent.
	Number.	Per cent.	Number.	Per cent.		
Over $+20$. . .	1	1	0	0	1	100.0
$+11$ to $+20$. . .	6	6	1	2	7	85.7
0 to $+10$. . .	25	25	8	13	33	75.7
-10 to -1 . . .	49	49	20	33	69	71.0
-20 to -11 . . .	19	19	21	35	40	47.5
Below -20 . . .	0	0	10	17	10	0.0
Total . . .	100	100	60	100	160	

The average index of resistance for the patients who recovered was -3.7 ; for those who died, -10.5 .

Discussion. Up to the present time, the prognostic significance of the differential leukocyte count has been carefully investigated in only a few diseases. Since the question of surgical interference clamors urgently for solution whenever the diagnosis of appendicitis is made, this disease has attracted more attention than any other in this connection. Gibson's general findings have been corroborated by a series of investigators.⁸ Other writers have usually chosen a mixed group of acute infectious diseases for their material. It is obvious that conclusions based on the results in a series of cases of acute appendicitis would not necessarily hold for diseases known to call forth peculiar blood responses on the part of the body. The leukopenia-producing diseases, for example, such as influenza and typhoid would require separate study. Since these particular leukopenias are characterized by suppression of polymorphonuclear leukocytes they would doubtless yield uniformly high indexes of resistance not justified by the 10 per cent mortality of typhoid fever. The high lymphocytic percentage in whooping cough and the peculiar blood picture of infectious mononucleosis could be cited as extreme examples of specific types of response of the organism to infections, nullifying attempts to apply prognostic data obtained from one disease indiscriminately to another.

On the other hand, there is a large group of acute infectious processes which usually call forth a polymorphonuclear leukocytosis apparently not of specific type. One might cite the pneumonias, scarlet fever, septicemia and puerperal sepsis, cerebrospinal fever, erysipelas, and the acute pyogenic infections such as appendicitis, peritonitis, mastoiditis, acute lymphadenitis, septic thrombophlebitis, etc. In these, the index of resistance might be expected to yield reasonably consistent prognostic data. It must not be forgotten,

however, that unexplained paradoxical variations are observed from time to time, justifying Wilson's⁹ remark that "No sweeping conclusions would be warranted from the . . . data." The present series of cases well illustrates this point.

The small group of patients, constituting 9 or 15 per cent of the fatal cases, who died in spite of indexes of resistance indicating a good outlook (positive or zero) are of especial interest. One can readily conceive of a patient with good resistance immunologically speaking who might nevertheless become exhausted from anoxemia due to wide-spread consolidation of the lungs. None of our cases decisively illustrates this possibility, however. Six of these 9 patients had their counts performed within forty-eight hours of death. Several writers¹⁰ have noted that moribund patients and children constitute two classes whose indexes of resistance are apt to be misleading. Walker made repeated determinations on 46 patients with pneumonia and noted that "in 6 out of 17 deaths, there was observed a sharp and marked antemortem rise to positive. This occurred usually from twenty-four to forty-eight hours prior to death." The exact reason for the death of our other 3 patients in spite of favorable early indexes is less apparent.

It is noteworthy that 68 per cent of the patients who recovered had negative indexes of resistance according to Walker's formula. Seemingly, to judge from our material, the formula is set at too low a pitch and might be altered to advantage in the direction of optimism. We therefore question the wisdom of Walker's alteration of Gibson's normal upper polymorphonuclear leukocyte level from 75 per cent to 70 per cent. Applying Walker's formula with the substitution of Gibson's figure raises any given index of resistance 5 points. In our series this would give an average index of resistance of +1.3 for those who recovered and -5.5 for the fatal cases. The use of such an altered formula would yield 56 per cent of favorable indexes (zero or plus) among the group who recovered and 72 per cent unfavorable (minus) among those who died. Such a readjustment seems to approach somewhat more nearly the balance Walker was aiming at when he originated the term and concept "index of resistance."

In suggesting this change we are aware that the normal differential leukocyte count rarely reveals 75 per cent of polymorphonuclear leukocytes and that Walker is therefore theoretically right. Apparently, however, in the presence of infection with good resistance the percentage of polymorphonuclears frequently rises somewhat more than one unit for every thousand increase in the total count above 10,000. The use of Gibson's higher figure of 75 per cent affords a convenient method of making approximate allowance for this.

Unfortunately, we are not able to claim extreme accuracy for the counts on which this study is based. They were made as a routine

duty by interns who had no idea their work was to be used for an analysis of a series of differential counts. Probably in few cases were more than 100 cells counted. Nevertheless, they are representative of differential counts as routinely done in hospital practice, and it is from such counts that deductions will usually have to be made by the attending physician or surgeon.

Conclusions. 1. Absence of leukocytosis is an unfavorable and leukopenia an ominous sign in lobar pneumonia. A high total leukocyte count, especially 20,000 per c.mm. or above, is reassuring.

2. Suppression of the total lymphocyte count below the low normal of 1200 per c.mm. is of bad import, having been noted in over half of the fatal cases.

3. Among 100 patients who recovered from pneumonia, 68 per cent had negative indexes of resistance at the initial blood count. A negative index of resistance cannot therefore be regarded *per se* as alarming. Nevertheless, a very low index of resistance is unfavorable.

4. A slight alteration of Walker's formula is suggested with the object of making it express more nearly the idea for which he designed it.

5. The specific nature of the body's response to various types of infection makes caution necessary in drawing prognostic conclusions from differential counts.

6. The initial total leukocyte and differential leukocyte counts are frequently useful in the prognosis of pneumonia. Paradoxical results are sufficiently common, however, to discourage undue dependence on their prognostic significance.

REFERENCES.

1. Weiss, A.: Newer Hematologic Aspects of the Neutrophils in Infections, *Am. J. Med. Sci.*, 1927, 174, 45.
 2. Reznikoff, Paul: Immature White Blood Cell Counts in Infectious Diseases, *J. Am. Med. Assn.*, 1929, 93, 963.
 3. Hinkleman, A. J.: The Differential Count in Acute Surgical Infections, *J. Kansas Med. Soc.*, 1925, 25, 363.
 4. Todd, J. C. and Sanford, A. H.: *Clinical Diagnosis by Laboratory Methods*, W. B. Saunders Company, 6th ed., 1927.
 5. Sondern, F. E.: The Present Status of Blood Examination in Surgical Diagnosis, *Med. Rec.*, 1905, 67, 452.
 6. Gibson, C. L.: The Value of the Differential Leukocyte Count in Acute Surgical Diseases, *Ann. Surg.*, 1906, 43, 485.
 7. Walker, O. J.: An Index of Body Resistance in Acute Inflammatory Processes, *J. Am. Med. Assn.*, 1919, 72, 1453.
 8. Wilson, L. B.: Value of Sondern's Differential Leukocyte Resistance Line in the Diagnosis and Prognosis of Acute Appendicitis, Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, 1905-1909, p. 280. Menninger, W. C. and Heim, H. S.: The Clinical Significance of the Relation of Total and Differential Leukocyte Counts in Acute Appendicitis, *Ann. Surg.*, 1924, 80, 915.
 9. Wilson, L. B.: *Loc. cit.*
 10. Sondern, F. E.: The Value of the Differential Leukocyte Count in Diagnosis, *Am. J. Med. Sci.*, 1906, 132, 889.
- Walker, O. J.: *Loc. cit.*

ANEURYSM OF THE CORONARY ARTERIES.

REPORT OF A CASE.

BY RALPH L. COX, M.D.,

RESIDENT PHYSICIAN, THE LAKESIDE HOSPITAL,

AND

CHESTER D. CHRISTIE, M.D.,

ASSISTANT CLINICAL PROFESSOR OF MEDICINE, SCHOOL OF MEDICINE, WESTERN RESERVE UNIVERSITY; ASSOCIATE PHYSICIAN, THE LAKESIDE HOSPITAL.

(From the Departments of Medicine and of Pathology of the School of Medicine of Western Reserve University and of the Lakeside Hospital, Cleveland.)

THE occurrence of aneurysm in the coronary arteries is exceedingly rare. Packard and Wechsler¹ have recently collected 29 cases from the literature, and have added 1 case of their own. Their study showed that the condition was two and a half times as frequent in men as in women. The age of the individuals in which these aneurysms occurred varied between five and seventy-seven, and averaged thirty-seven years. The aneurysms were usually single, and were situated most frequently in the left coronary artery within the first 3 cm. of its course. Rupture of the aneurysm was reported in 12 of the 29 cases in which this phenomenon was mentioned.

The symptomatology of this disease is not typical. Two major types have been observed. In the first of these the patients present a history referable to rheumatic heart disease, usually with a bacterial endocarditis superimposed upon damage due to previous rheumatic infection. In the second type there is the syndrome of angina pectoris or of myocardial degeneration as a result of disease of the coronary arteries. Physical examination reveals nothing that is characteristic. The mode of death is variable. The ante-mortem diagnosis of coronary aneurysm is, obviously, not possible.

Many of these aneurysms (about 35 per cent) are not classifiable etiologically, due to the varied picture which they present. The apparent etiologic factor most frequently observed (42 per cent) is arteriosclerosis. A second major group (23 per cent) consists of the mycotic-embolic aneurysms, which occur in association with an acute or subacute bacterial endocarditis of the aortic valve. Judging from the associated incidence of syphilitic mesaortitis, which occurred in only 3 of the 31 cases, syphilis is not an important factor in the etiology of aneurysms in this location. The rôle of trauma in the production of coronary aneurysms is not significant.

Packard and Wechsler considered 12 of their series of cases to be unquestionably arteriosclerotic in origin. The case reported here is believed to belong also in this classification. Eleven of these 13

were men, and 2 were women. The age of these individuals varied between thirty-two and seventy-seven, and averaged fifty-six years. In only 3 of the cases, including the 1 here presented, was the aneurysm situated in the right coronary artery. The size of the aneurysms varied between that of a "pea," and 6 cm. in diameter. Rupture of the aneurysm occurred in 5 cases, and was not mentioned in one of the reports. There was a variable mode of death. Seven, including those 5 in which rupture occurred, died suddenly. Three died with symptoms and signs referable to gradual cardiac failure. One died of intercurrent infection, while the manner in which the remaining 2 died was not noted.

Case Report.—A. B. E., a native-born white man, aged sixty-five years, a broker, was seen by one of us (C. D. C.) on May 31, 1929, with complaints of shortness of breath and of generalized swelling. He had always felt well until a few months before the date mentioned. He had known, however, that he had had an elevated blood pressure (180 to 200 systolic) for many years. In January, 1929, he had had a "stroke," involving the entire left side of the body, from which he had recovered sufficiently to be able to move about the house with the aid of a crutch and a cane. He had lost about 20 kg. during the preceding year.

Physical examination revealed a well-developed, somewhat undernourished male. The left side was paretic. There was marked respiratory distress, with periodicity of the Cheyne-Stokes type. The lungs were clear. There was a slight degree of cardiac enlargement, and a systolic murmur was audible at the apex and over the aortic area. The heart was otherwise normal. The palpable arteries were tortuous and sclerotic, but the ocular fundi showed no abnormalities. The pulse rate was 100; the blood pressure 150 systolic, 80 diastolic. The abdomen was normal. There was a considerable degree of edema, involving chiefly the lower extremities.

The urine contained a trace of albumin. The blood urica was 33 mg. The patient was put to bed, digitalized, and given metaphyllin by mouth. His respiratory mechanism became normal. The edema gradually disappeared. He then weighed about 75 kg. After ten days of bed rest, he was allowed to be up. His blood pressure was still 150 systolic, 80 diastolic, with a pulse rate of 75.

Two weeks later, the patient complained of moderate abdominal discomfort. Physical examination was essentially as it had been, although the abdomen was somewhat distended. Later that day the patient relapsed into a condition of shock, with a pulse rate of 130 and a blood pressure of 80 systolic, 50 diastolic. There was extreme Cheyne-Stokes periodicity, with apneic periods lasting sometimes as long as one minute and nine seconds. The abdomen was markedly distended. On the following evening abdominal distention had disappeared, and a pulsatile tumor, about 10 cm. in diameter, was felt about the point of bifurcation of the abdominal aorta.

Contrary to expectation, the patient gradually improved, and was again able to be up about the house. The blood pressure, however, never resumed its former level, the systolic pressure varying between 70 and 95. About two months later, edema of the extremities reappeared, and respiratory periodicity was again troublesome. From then on the patient's course was constantly downward. There was gradual enlargement of the heart sufficient to place the left border of cardiac dullness outside of the anterior axillary line. There was increasing mental confusion, and the patient was difficult to control. During the last three weeks it was impossible to give him anything by mouth. His edema then became less, the urinary output

was markedly reduced, and he lost weight rapidly. He was moribund for several days, and died October 21, 1929.

*Autopsy Report.** The body, weighing approximately 52 kg. and about 175 cm. long, was that of an emaciated white male appearing to be about sixty-five years of age. There were several decubital ulcers over the sacrum, buttocks and heels. There was nothing else of interest on external examination except an asymmetry of the lower abdomen produced by an intra-abdominal tumor mass which caused a firm nodular elevation, about 6 cm. in circumference, below and to the right of the umbilicus.

The examination was limited to an abdominal incision. On section, no abnormalities of the subcutaneous tissues or of the serous cavities were observed.

The heart weighed 500 gm. Hypertrophy and dilatation were generalized, but particularly marked on the left side. The myocardium at the apex, and extending upward anteriorly, laterally and posteriorly for several centimeters, had been replaced by dense fibrous connective tissue. The wall at the apex itself was not more than 3 mm. thick. The endocardium over this extensive area of myocardial cicatrization was opaque and fibrous. The right ventricular wall measured about 5 mm. in thickness. The septum was thin and the septal endocardium was thick and fibrous. The papillary muscles and the columnæ carneæ were atrophic and flattened. No intra-ventricular thrombosis was present. The valves and valve orifices showed only a moderate degree of sclerosis.

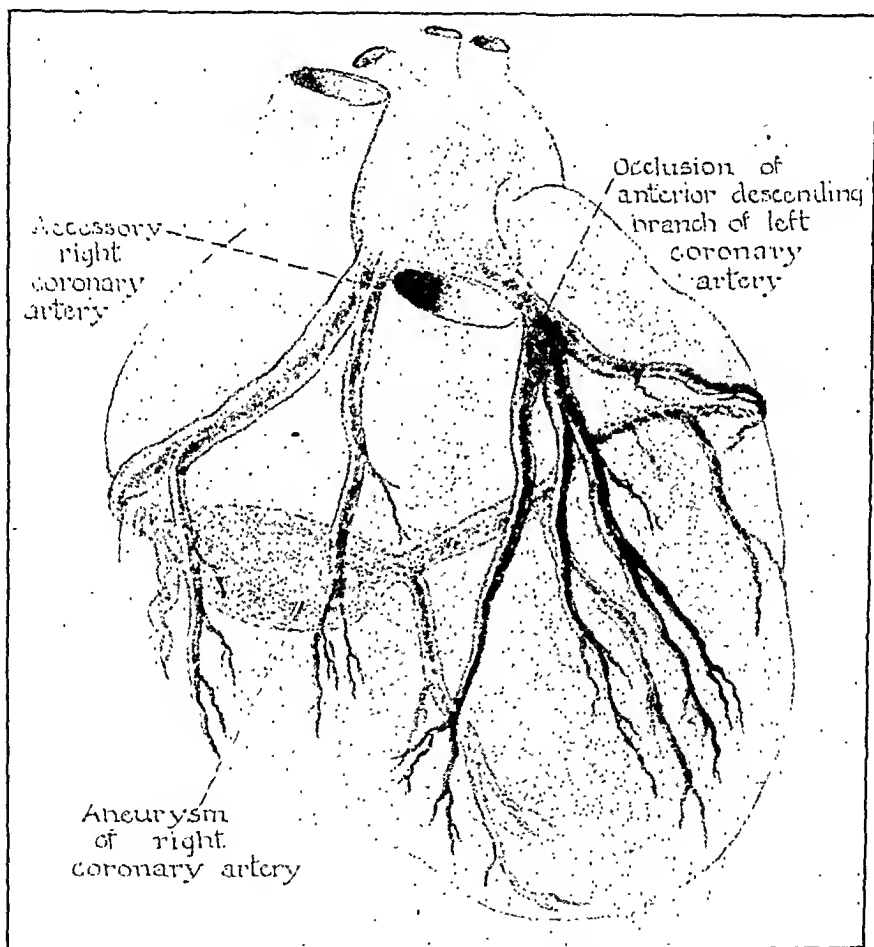
The coronary orifices were not unusual. The left circumflex branch was small but patent. The left ramus descendens, just below its origin, was completely occluded by old organized thrombosis in a segment the seat of advanced arteriosclerosis and calcification. The first branch of the right coronary artery had an anomalous origin direct from the anterior aortic sinus. The main trunk of the vessel was unusually large, having an average diameter of about 7 mm. until it had reached the posterior aspect of the right ventricle, where, in the medial atrioventricular groove, there was a spindle shaped dilatation. (See illus.) The maximum diameter of this dilatation was 2.5 cm. and it extended a distance of 4.5 cm., stopping abruptly at the junction of the interventricular septum posteriorly. There was no thrombosis in this aneurysm. Large branches of the right coronary artery coursed obliquely across the posterior aspect of the left ventricle. The main trunk of the vessel continued, with a diameter of about 6 mm., in the left atrioventricular sulcus, and extended beyond the termination of the left circumflex branch. The right coronary artery was patent throughout its course. The entire coronary circulation was characterized by the tortuosity of the secondary branches, by the extreme degree of calcification, and by the nodular inequalities in the circumferences of the vessels.

The thoracic aorta had an average diameter of 8.5 cm. in the ascending portion. It showed a moderate degree of arteriosclerosis, with very little calcification and no gross evidence of aortitis. The abdominal aorta presented a picture of marked and extensive atherosclerosis, with calcification, ulceration and intimal thrombosis. There were a number of small pouch-like dilatations of the wall. Immediately below the origin of the inferior mesenteric artery, and extending from there to the bifurcation, there was a sacular dilatation of the aorta, measuring 11 cm. in diameter. This dilatation was eccentric, lying mostly to the right. The sac was almost entirely filled with lamellar thrombus, and this thrombosis extended somewhat above and below.

The branches of the abdominal aorta showed a similar degree of sclerosis and nodular inequalities in their circumferences. The celiac axis had a

* We are indebted to Dr. Alan R. Moritz, the pathologist of the Lakeside Hospital, for the privilege of reporting these findings.

diameter of 1 cm. at its origin, 14 mm. at its first division, and its gastro-hepatic branch terminated in three hepatic branches with average diameters of 5 mm. The superior mesenteric artery reached, in places, a diameter of 13 mm.; in other places it did not exceed 1 cm. The inferior mesenteric and the renal arteries revealed similar changes. The common iliac arteries arose directly from the inferior pole of the aortic aneurysm. The left had a fairly uniform diameter of about 2 cm., but the right varied between 1.5 cm. at its origin and 3.5 cm. a little farther along. Both of these arteries were the seat of thrombosis, the clot being continuous with that in the aneurysmal sac.



Aneurysm of the right coronary artery, presumably arteriosclerotic in origin. There was severe generalized arteriosclerosis. The ramus descendens of the left coronary artery was obliterated by organized thrombosis, with resulting myocardial infarction.

The inferior vena cava was firmly adherent to the surface of the aortic aneurysm. It was collapsed and stretched to such an extent that its intimal surfaces were closely approximated, but there was no thrombosis. The left renal vein was completely obliterated by organized clot.

The liver weighed 900 gm. Except for atrophy and for the unusually small hepatic arteries, there was no pathologic change.

The kidneys weighed, together, 200 gm. Their contour was grossly

irregular, and in addition to both coarse and fine granularity of their surfaces, there was evidence of multiple old and recent infarction. The cortex was reduced and variable in width.

Histologic sections of the heart, cut so as to include branches of the coronary arteries, showed marked intimal thickening of the vessels, with extensive hyaline degeneration and calcification. In some instances the degeneration was limited to the intima but in other areas the entire wall of the vessel appeared to be involved. Little or no inflammatory reaction was noted in connection with this sclerosis. The sclerotic changes were relatively less severe in the smaller branches. The lumina of the arteries were reduced in size to a varying degree, even to obliteration. The myocardium was characterized by large areas of cicatrization, some of which were recent and showed fibroblastic proliferation and vascularization, while others were older and showed complete replacement of muscle by dense hyalinized scar tissue.

Sections from the aorta showed great thickening of the intima, with hyaline and fatty degeneration, and areas of necrosis filled with structureless granular material. Acicular spaces in this necrotic material suggested the sites of crystalline deposition. The surface of the intima was roughened, and attached to these roughened surfaces were thrombus masses. The media showed extensive calcification and hyaline and myxomatous degeneration, which in some places closely approached the adventitia. In one large plaque of medial calcification true bone formation was observed. Throughout the aorta and the medium-sized arteries there was extensive interruption of continuity of the elastica. The adventitia showed considerable focal lymphocytic infiltration, with some tendency to perivascular distribution, but the vasa vasorum did not show obliteration. Where the focal degeneration of the media bordered on the adventitia there was, in some instances, organization, as manifested by loose granulation tissue extending from the adventitia into the necrotic areas.

The pathologic diagnosis was: aneurysm of the right coronary artery; aneurysm of the abdominal aorta; aneurysm of the right common iliac artery; generalized arteriosclerosis, severe; thrombosis and obliteration of the ramus descendens of the left coronary artery; atheromatous ulceration and intimal thrombosis of the aorta; thrombosis of the common iliac arteries; thrombosis of the left renal vein; infarction of the myocardium; infarction of the kidneys; cardiac hypertrophy and dilatation; arterial and arteriolar nephrosclerosis; anomaly of the right aortic sinus; atrophy of the liver; decubital ulcers; emaciation.

The pathologic changes in the arteries were essentially degenerative, and were most pronounced in the media. There was accompanying degeneration and productive inflammation of the intima. This inflammation appeared to be secondary to the degeneration. Fragmentation of the elastica was prominent, and seemed to be spontaneous rather than the result of inflammatory destruction. This deterioration of the elastica presumably permitted a generalized dilatation of the larger bloodvessels, which in three instances was of aneurysmal size.

Summary. 1. A case of aneurysm of the right coronary artery is reported.

2. There were no clinical findings suggesting this lesion.

3. In addition to the coronary aneurysm, and to nodular inequalities in the circumferences of the medium-sized arteries, there was a large saccular aneurysm of the abdominal aorta, and a fusiform aneurysm of the right common iliac artery. There was an extreme

degree of sclerosis of the coronary arteries, with occlusion of the left ramus descendens and extensive myocardial infarction.

4. This is the thirty-first instance which we have found in the literature of aneurysm of the coronary arteries.

REFERENCE.

1. Packard, Mauriee; and Wechsler, H. F.: Aneurysm of the Coronary Arteries, *Arch. Int. Med.*, 1929, 43, 1.

THE SIGNIFICANCE OF SINUS ARRHYTHMIA IN OLD PEOPLE.

BY JAMES M. FAULKNER, M.D.,

JUNIOR VISITING PHYSICIAN, BOSTON CITY HOSPITAL; ASSISTANT IN MEDICINE,
HARVARD MEDICAL SCHOOL, BOSTON.

(From the Thorndike Memorial Laboratory and Fourth Medical Service, Boston City Hospital, and the Department of Medicine, Harvard Medical School, and the Cardiographic Laboratory, Johns Hopkins Hospital.)

It is the purpose of this paper to call attention to a type of sinus arrhythmia occurring in old people which, in contradistinction to the type seen in youth, appears to have some pathologic significance.

Sinus arrhythmia is an irregularity in the cardiac rhythm resulting from changing rates of discharge of impulses in the sinoauricular node. The cardiac rate at any given moment is the resultant of two forces acting on this node—the vagus and the sympathetic. In young people it is periodic alterations in vagal tone associated with the phases of respiration which produce the alternate acceleration and deceleration of the heart rate, known as sinus arrhythmia. Einthoven¹ clearly demonstrated the reflex nature of this phenomenon in 1908. He showed that sinus arrhythmia was abolished by atropin or by vagal section, and he recorded by means of the string galvanometer rhythmic action currents passing up the vagus nerve in the dog (Chart 1). These action currents have a double rhythm, consisting of large, slow oscillations corresponding with the respiratory rate, and small, rapid oscillations corresponding with the heart rate. In rabbits, where the depressor nerve is separate from the vagus, he demonstrated that the vagus nerve shows exclusively respiratory oscillations while the depressor nerve shows only heart beat oscillations. Stimulation of the central end of either vagus or depressor nerve causes slowing of the heart. Of these two reflex mechanisms in the healthy heart it is apparently only the afferent impulses from the respiratory system which reach a magnitude sufficient to alter the cardiac rhythm.

As to the clinical significance of this irregularity, it has been generally regarded to have no pathologic significance and, indeed,

to be a favorable prognostic sign if found in the presence of heart disease.² Sir James Mackenzie³ stated that he has "Never seen the presence of this irregularity in an acute infection or with a progressive lesion of the heart muscle."

However, Wedd,⁴ in 1921, stated that sinus arrhythmia may not only exist in the presence of organic heart disease but may actually be a manifestation of it. He appears to have been the first to point out the possible rôle of afferent impulses from a diseased heart or aorta in producing sinus arrhythmia. Wedd says: "Just as in certain pathologic states impulses may arise in the heart which give rise to sensations of pain, so it is believed that in other abnormal conditions impulses may form in the heart or aorta, which, transmitted by the afferent fibers of the vagus of the cardiac depression nerve to the inhibitory center, will become manifest as disturbances of the cardiac mechanism."

There follows a summary of 4 cases of sinus arrhythmia in the presence of arteriosclerotic heart disease which have come under my observation.

Case Reports. CASE I.—A male, aged eighty-seven years (Johns Hopkins Hosp. Ecg. No. 6271), was moribund and died within twenty-four hours of his entrance to the hospital. A satisfactory history was not obtained. Physical examination showed general anasarca to be present. The heart was enlarged to the left by percussion. Its sounds were weak and totally irregular. The blood pressure was 88/60. The urine contained a trace of albumin. The nonprotein nitrogen in the blood was 32 mg. per 100 cc. Phthalein test 14 per cent excreted in two hours. An electrocardiogram showed marked sinus arrhythmia; partial heart block; *P-R* interval 0.23 seconds; *Q-S* interval 0.08 seconds; some slurring of *Q-R-S* in all leads. *T* wave inverted in all leads.

A diagnosis was made of arteriosclerotic heart disease, myocardial insufficiency and carcinoma of the prostate.

CASE II.—A male, aged seventy years (Boston City Hosp. No. 571253), entered the hospital complaining of productive cough of several days' duration. He had suffered from increasing dyspnea for about five years.

Physical examination showed marked peripheral arteriosclerosis, a barrel-shaped chest, and musical and crepitant râles at the bases of the lungs. The heart appeared to be enlarged slightly and presented a curious irregularity consisting of runs of 10 or 12 rapid beats alternating with 10 or 12 slow beats. The blood pressure was 120/60. There was no peripheral edema. An electrocardiogram on day of admission showed marked sinus arrhythmia, rate 80 to 90, *P-R* interval 0.14 seconds, *Q-S* interval 0.08 seconds. *T*-wave upright in all leads. Two days later the arrhythmia was less marked and nine days later it had disappeared altogether. The patient improved on rest in bed and was discharged after one month with a diagnosis of acute bronchitis, arteriosclerosis, chronic myocarditis, sinus arrhythmia. Both bronchopneumonia and pulmonary tuberculosis were considered to be perhaps present in addition.

CASE III.—A male, aged sixty-one years (Boston City Hosp. No. 577915), entered the hospital complaining of chill and productive cough. He gave a history of a number of attacks of severe precordial pain associated with

dyspnea which were not brought on by exertion. He had no dyspnea on exertion.

Physical examination showed well-marked peripheral arteriosclerosis and emphysema. There were many crepitant and musical râles throughout both lungs. There was no peripheral edema. A Roentgen ray examination of the chest showed enlargement of the heart to the left but a "seven-foot plate" was not taken. Electrocardiograms showed marked sinus arrhythmia, rate 50 to 60, *P-R* interval 0.16 seconds, *Q-S* interval 0.12 seconds; *T* wave diphasic in Lead I, upright in Lead II, and low in Lead III. The *Q-R-S* complexes were slurred in all leads. The electrocardiographic diagnosis was: sinus arrhythmia, intraventricular block with perhaps right bundle branch block.

By means of synchronous pneumographic and electrocardiographic records it was possible to demonstrate graphically in this case what had been suspected to occur in the two previous cases, namely, that the cardiac rhythm bore no relation to the phases of respiration. Indeed, there were at times long periods of bigeminal rhythm due to sinus arrhythmia. Inhalation of amyl nitrate sufficient to lower the blood pressure from 110/70 to 90/60 and to raise the pulse rate from 60 per minute to 80, caused no decrease of the arrhythmia. Vagal pressure produced marked slowing of the heart rate with ventricular escape. After administration of atropin sulphate, 1/60 gr. (0.001 gm.) intravenously, the heart rhythm became regular at a rate of 72 and vagal pressure no longer produced slowing.

This patient's arrhythmia persisted during the six weeks he stayed in the hospital.

He was considered to have bronchopneumonia, bronchial asthma, arteriosclerotic heart disease, coronary sclerosis, and generalized arteriosclerosis.

CASE IV.—A male, aged seventy-five years (Boston City Hosp. No. 579673), complained of shortness of breath and precordial pain on exertion. He had rheumatic fever at the age of eighteen years but did not experience any symptoms of cardiac disease, until five years ago, when he began to have substernal pain on exertion with moderate degree of dyspnea and edema of the ankles. This man was treated in a hospital for cardiac decompensation at that time, when the cardiac rhythm was noted to be regular. In the course of five hospital admissions the physical signs in the heart underwent an interesting evolution. On the first admission only a high-pitched systolic murmur maximal in the aortic area and transmitted over the entire precordium was heard. On the third admission a thrill was felt over the aortic area and a faint early diastolic murmur at the apex of the heart. On the fourth admission the rhythm was irregular, and on the fifth and last admission the above signs were all present in addition to diastolic murmurs in both the aortic and mitral areas. The patient had also extensive peripheral arteriosclerosis, cyanosis, and moist râles at the bases of both lungs. The heart was markedly enlarged to the left, as shown by a "seven-foot Roentgen ray plate" (transverse diameter of heart 19.2 cm., internal diameter of thorax 28 cm.). An electrocardiogram showed sinus arrhythmia with a heart rate approximately 65, partial heart block *P-R* interval 0.28 seconds, intraventricular block, *Q-S* interval 0.11 seconds. Slurring or notching of *Q-R-S* complex occurred in all leads. The *T* wave was inverted in Lead I, upright in Leads II and III. Synchronous pneumographic and electrocardiographic records showed that there was generally an acceleration of the cardiac rate with inspiration and slowing with expiration. Admission of 1/40 gr. (0.0015 gm.) of atropin sulphate intravenously raised the cardiac rate from 48 to 60 beats per minute, and lessened, but did not abolish, the arrhythmia. It did not alter the *A-V* conduction. This patient had no attacks of angina pectoris while in the hospital. The

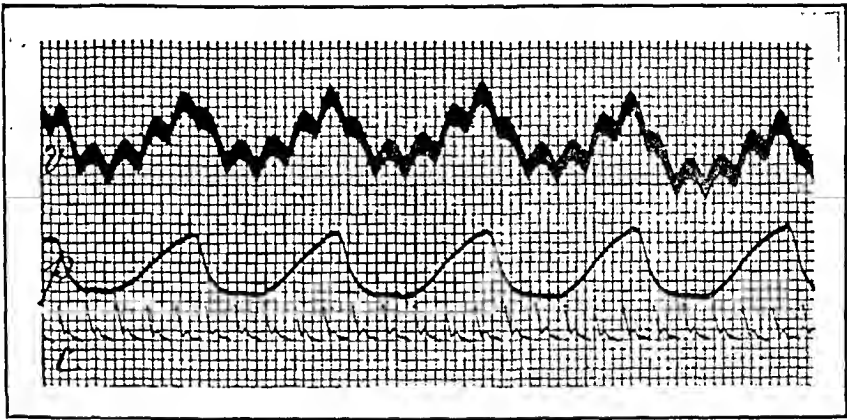


CHART 1.—Figure showing the electrical changes in the vagus nerve which accompany the respiratory and heart movements. *v*, Electrovagogram; *p*, respiration record (ascent of curve, inspiration; descent, expiration); *c*, pulse record. (After Einthoven.)

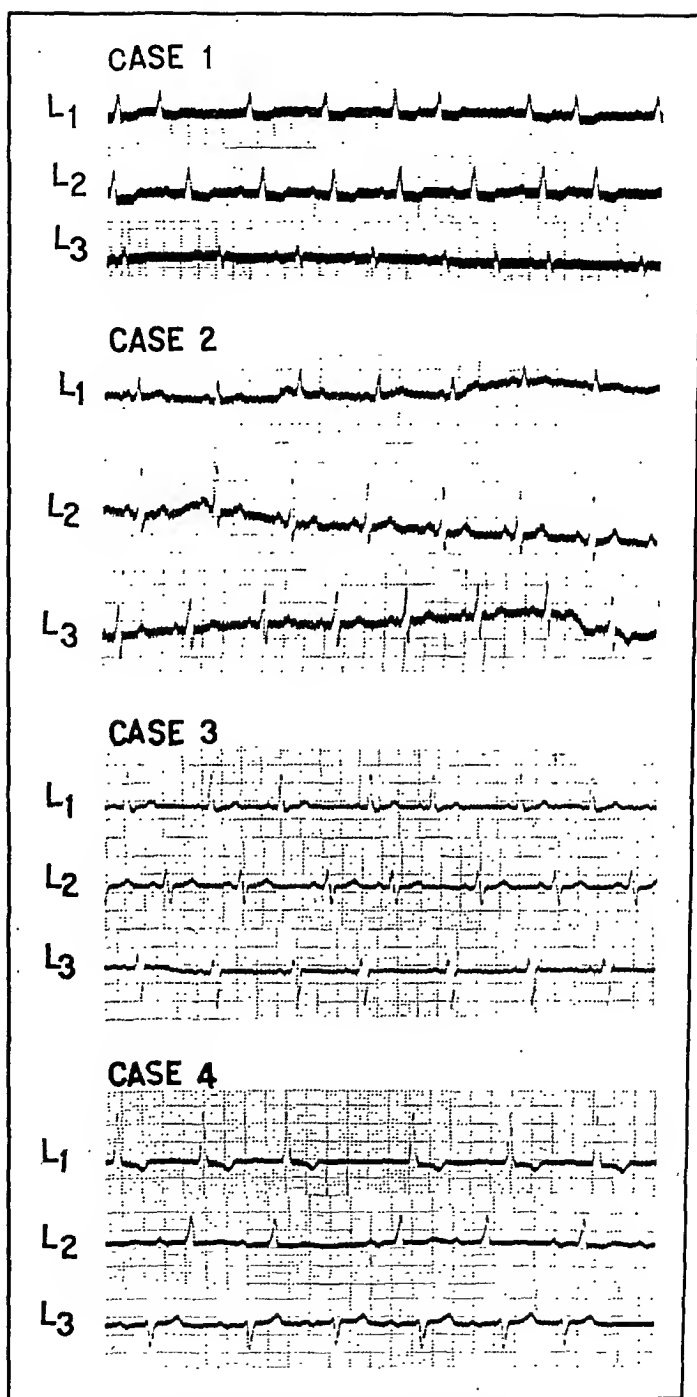


CHART 2.—Electrocardiograms of 4 cases of sinus arrhythmia in old people. See text.
Customary lead and standardization.

arrhythmia persisted but the dyspnea gradually subsided; the râles disappeared from his lungs; and after six weeks he was discharged from the hospital with the diagnosis of aortic stenosis and regurgitation, mitral stenosis and regurgitation, cardiac decompensation, generalized arteriosclerosis, rheumatic heart disease (?), arteriosclerotic heart disease (?), asthmatic bronchitis, emphysema, partial heart block, and sinus arrhythmia.

Discussion. The observation of this "benign, youthful irregularity," as Mackenzie termed it, in older people with advanced organic heart disease, led me to examine hospital records in order to determine its incidence and, if possible, its clinical significance. For this purpose I have analyzed all the cases with an electrocardiographic diagnosis of sinus arrhythmia at the Johns Hopkins Hospital, and all such cases over fifty years of age at the Boston City Hospital.

At the onset all cases showing auricular extrasystoles were excluded because it was believed that sinus arrhythmia in association with these ectopic contractions is a secondary phenomenon brought about by extrasystolic beats. It was also recognized that sinus arrhythmia is not infrequently seen for varying periods following reversion to sinus rhythm after auricular fibrillation, auricular flutter or paroxysmal auricular tachycardia, whether the reversion be induced by drugs, such as quinidin or digitalis, or whether it be spontaneous. Under these circumstances sinus arrhythmia does not perhaps have the same significance as when it is not preceded by an abnormal rhythm. It has been impossible to exclude such cases from this series, however, because a large percentage of elderly patients with sinus arrhythmia come to the cardiographic laboratory with a mistaken clinical diagnosis of auricular fibrillation.

Digitalis in large doses is said at times to cause disturbance of the sinus rhythm, but it does not appear to be an important factor in this series because in only 1 case of sinus arrhythmia was there recorded clinical evidence of digitalis poisoning.

In the electrocardiographic records of the Johns Hopkins Hospital up to August, 1927, there were 138 cases of sinus arrhythmia, amounting to 4 per cent of the total electrocardiograms taken. These records show a decreasing incidence of sinus arrhythmia with advancing years. In patients under thirty-five years the incidence is about 12 per cent. Above the age of thirty-five years the incidence drops down to about 5 per cent and above the age of fifty years sinus arrhythmia is rare, occurring in only 23 cases or 1 per cent of the total cases above that age.

In the group of patients under fifty years of age the most common clinical diagnosis was hyperthyroidism. This diagnosis was established for 18 cases (17 per cent). Rheumatic heart disease was the next most frequent diagnosis, with 8 cases (8 per cent). Luetic heart disease was present in 5 cases (5 per cent). In the patients over fifty years of age naturally arteriosclerotic heart disease was the most common diagnosis, occurring in 33 per cent of the cases.

Hypertensive heart disease and luetic heart disease formed 16 per cent of the cases in the older patients. Myxedema was the diagnosis for 1 case.

A more striking contrast between the two groups is obtained if one considers the number of cases in each group that showed presumptive evidence of organic cardiac disease on physical examination, or by electrocardiographic examination. The criteria used were, briefly, the presence of undoubted signs of congestive heart failure, diastolic murmurs, pulsus alternans, cardiac enlargement or aortic dilatation as determined by Roentgen ray examination or by electrocardiographic demonstration of *A-V* block, intraventricular block, or inversion of the *T* wave in Lead II in the absence of digitalis therapy. Twenty-four per cent of the younger patients showed presumptive evidence of organic cardiac disease, and only 10 per cent had congestive failure. This is in contrast to the patients over fifty years of age, of whom 65 per cent had evidence of organic heart disease and 33 per cent had congestive failure.

At the Boston City Hospital satisfactory records were available for 22 patients with sinus arrhythmia over fifty years of age. Sixteen of the patients had arteriosclerotic heart disease, 4 had luetic heart disease and 2 had rheumatic heart disease. Four of these individuals suffered from angina pectoris. The last patient to be accounted for had myxedema. In this case the sinus arrhythmia disappeared under thyroid extract therapy coincident with which there was a return of the low electrocardiographic complexes to normal height.

For comparison the records of 100 ward patients over fifty years of age who showed sinus rhythm by electrocardiogram were picked at random from the files and studied. It was found that 23 patients, or 85 per cent of those with sinus arrhythmia showed presumptive evidence of organic heart disease, as compared to 57 per cent of the 100 patients with normal cardiac rhythm. The percentage of cases with signs of congestive failure was slightly higher in the sinus arrhythmia group, totaling 14 cases, or 50 per cent as compared to 46 per cent of the normal rhythm group.

The above figures appear to indicate that sinus arrhythmia is not always a benign irregularity, for, in older people, it is more apt to be associated with organic heart disease than is normal rhythm. This type of sinus arrhythmia found in old people, in marked contrast to the youthful type of sinus irregularity, is often met with in the presence of advanced and progressive heart disease. An additional distinguishing feature is that the sinus irregularity of old age frequently bears no relation to the phases of respiration. These findings suggest the probability that there are two distinct types of sinus arrhythmia, having a different mode of origin—a youthful type which is directly related to normal phasic variations in vagal tone corresponding to the phases of respiration, and a type

seen in older people which may bear no relation to the respiratory rhythm and which, indeed, may be a response to abnormal afferent impulses arising in a diseased heart or aorta.

Summary. 1. The pathologic significance of 4 cases of sinus arrhythmia in old people with organic heart disease is discussed.

2. Analysis of hospital records shows that sinus arrhythmia in patients over fifty years of age is more frequently associated with evidence of organic heart disease than is normal rhythm.

3. Support is lent to the suggestion of Wedd that sinus arrhythmia may at times represent a reflex response to abnormal efferent stimuli from a diseased heart or aorta.

BIBLIOGRAPHY.

1. Einthoven, W.: On Vagus Currents Examined with the String Galvanometer, *Quart. J. Exp. Physiol.*, 1908, 1, 243.

2. McCrudden, Francis H.: Sinus Respiratory Arrhythmia in Children with Rheumatic Heart Disease, *J. Am. Med. Assn.*, 1926, 86, 535.

3. Mackenzie, Sir James: *Diseases of the Heart*, Third edition, Oxford University Press, London, 1921, p. 187.

4. Wedd, A. M.: Neurogenic Irregularities of the Heart in Adults, *AM. J. MED. SCI.*, 1921, 162, 49.

THE SYMPTOMATOLOGY OF ARTERIAL HYPERTENSION.

BY JOSEPH E. F. RISEMAN, M.D.,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.)

The Complaints of Patients With Uncomplicated Hypertension. The greater part of our knowledge of essential hypertension dates back less than twenty years. During this short period a close connection has been demonstrated between persistently elevated blood pressure and pathologic changes in the kidney, heart, brain and bloodvessels. The existence of hypertension can easily be determined with the sphygmomanometer, but it is frequently difficult to prove the presence of complications, especially in their incipient stage. This often can be done, however, by a critical analysis of all the information derived from the patient's clinical history, from a careful physical examination, and from the laboratory tests performed on the blood and urine.

Perhaps because of the ease with which the diagnosis of hypertension can be made and possibly because the condition has been studied intensively for less than two decades, relatively little attention has been paid to the symptomatology which accompanies high

blood pressure. There are few reports which state the frequency with which symptoms have been found (Table I). Even these

TABLE I.—SYMPTOMATOLOGY OF HYPERTENSION.

Kauffmann ¹ 48 cases.		Schultz and Bieln ² 114 cases.		Paullin, Bowcock, Wood ³ 500 cases.		Douthwaite ⁴ 43 cases.	
Symptom.	Per cent of cases.	Symptom.	Per cent of cases.	Symptom.	Per cent of cases.	Symptom.	Per cent of cases.
"Rheumatism"	68.4	Restlessness	29.8	Nocturia	49.0	Dyspnea	55.4
Dizziness	58.2	Insomnia	28.0	Cerebral crises	11.2	Palpitation	51.2
Hypersensitivity to warmth	47.9	Palpitation	22.8	Dyspnea	11.0	Headache	44.2
"Migraine"	43.8	Generalized fatigue	16.7	Angina pectoris	8.4	Giddiness	23.3
Morning headache	33.3	Constipation	16.7	Substernal oppression	5.6	Tinnitus	20.7
Angiospasm	12.5	Depression	16.7	Vertigo	3.6	Hemorrhage	13.9
		Dyspnea	14.0	Tinnitus	3.4	Sense of choking	9.3
		Irritability	14.0	Hemorrhage: Nasal	3.0	Angina	4.6
		Pressure on the head	13.2	Conjunctival	1.2	Miscellaneous	
		No desire to work	13.2	Uterine	0.8	Indigestion	
		Fatigue of arms	11.4	Pulmonary	0.2	Fleeting pains	
		Rheumatic complaints	10.5	Intestinal	0.2	Loss of memory	
		Fatigue of legs	10.5	Intermittent claudication	0.6	Nervousness	
		Anxiety	9.6			Insomnia	
		Dizziness	8.8			Nocturia	
		Migraine	7.9				
		Tinnitus	5.3				
		Boring headache	4.4				
		Poor memory	3.5				
		Early generalized fatigue	2.6				
		Loss of appetite	2.6				
		Sleepiness	2.6				
		Sensitivity to poor ventilation	1.7				
		No symptoms	8.8				

reports fail to differentiate between the early and late symptoms of hypertension and to throw light on the general significance of the symptoms observed. There is also a lack of knowledge concerning the relationship between the symptoms referable to hypertension and those observed in other diseases. Kauffmann¹, Schultz and Bieln,² Paullin, Bowcock and Wood,³ and Douthwaite⁴ have examined the histories of patients with hypertension and have reported the symptomatology. These four investigations together include about 700 cases; but 500 of these cases, studied by Paullin, Bowcock, and Wood,³ were studied from the point of view of the complications of hypertension, and therefore the symptoms exhibited by this group of patients may well bear rather on the cerebral, cardiac or renal complications, than on hypertension in itself. We have included in Table I those subjective symptoms which they listed as complications.

The symptomatology which we are to present here is based on an analysis of the records of 1090 uncomplicated cases* selected from the 1628 cases of hypertension discovered among the patients visiting the medical outpatient department of the Boston City Hospital during the forty-two months from January, 1926, to June, 1929, inclusive. So far as hypertension is concerned, outpatient cases are relatively free from the disabling complications of this condition seen in the majority of patients with hypertension who enter hospital wards. This situation is of advantage in determining the symptomatology of arterial hypertension *per se*, for the histories of cases with complications deal in the main with the symptomatology of the complicating pathologic condition. It was, then, to obtain complete records of uncomplicated cases of hypertension that the records of 538 patients were discarded.

The 1090 records then remaining represented cases of uncomplicated hypertension whose case histories were adequate and reliable. These cases were made up of 289 men and 801 women. The systolic pressure was 160 mm. Hg. or above in 90.2 per cent of the instances; the diastolic pressure was 100 mm. Hg. or above in 64.5 per cent of the cases. The blood pressure was observed to be elevated on repeated occasions.

TABLE II.—SYMPTOMATOLOGY OF HYPERTENSION. BASED ON THE RECORDS OF 1090 PATIENTS WITH ELEVATED BLOOD PRESSURE AND NO RELATED DISEASE.

Symptom.	Number of cases.	Per cent of 1090.
Headache	473	43.3
Dizziness	440	40.3
Aches and pains	422	38.7
Dyspnea	302	27.7
Nycturia	283	25.9
Nervousness	144	13.2
Palpitation	143	13.1
Tinnitus	129	11.8
Weakness	126	11.6
Insomnia	61	5.6
Epistaxis	61	5.6
Precordial pain	58	5.3
Numbness and tingling	48	4.4
Edema	46	4.2
Spots before the eyes	44	4.0
Hot flashes	24	2.2
Cramps	17	1.6
Nausea or vomiting	13	1.2
Blurred vision	11	1.0
"Angiospasm"	9	0.8
Throbbing	7	0.6
Hemoptysis	6	0.6
Fainting spells	6	0.6
No symptoms	129	11.8

* The term uncomplicated hypertension is used to define persistently elevated arterial blood pressure of the greater circuit without clinical evidence of impaired cerebral, cardiac or kidney function.

The symptoms which occurred in these cases are presented in Table II in the order of the frequency with which they were recorded. It is obvious that an analysis of records obtained by different individuals does not give such detailed and exact information as that of records taken by the same individuals especially interested and experienced in the disease. Doubtless the percentage frequency of many of these symptoms would be higher in a series of cases which could be followed over a long period of time or in cases where the existence of each of these symptoms was specifically searched for in each patient.

Headaches occurred in 43.3 per cent of the cases. The location varied but the headache was constant for each individual. The discomfort occurred at any time of the day but was most frequently noted in the early morning or evening. The character varied from sharp to dull pain, but it was usually steady; less frequently did a patient complain of a throbbing headache.

Dizziness, a symptom which was almost as frequent (40.3 per cent), occurred in varying degrees of severity but was always very distressing to the patient. Usually it consisted of a sense of giddiness or light headedness but occasionally there was true vertigo. Caloric ear tests when performed were uniformly negative. The dizziness was brought on or accentuated by change of position. This was the outstanding characteristic of the symptom. Although dizziness occurred at any time of the day, it was most frequent immediately after rising in the morning and after retiring at night. Dizziness and headache commonly occurred together or alternately in the same individual. This was the case for 60 per cent of the patients who had headaches and for 64.8 per cent of those with dizziness.

Somatic Aches and Pains were distressing to both patient and examiner, for no adequate cause could be found and no treatment gave more than temporary relief. The pains were of various sorts—sharp, dull, or aching, but usually vague and indescribable. The location and distribution were bizarre: in some cases they were limited to one small region, in other instances they were generalized or migrating from one spot to another, while in still others the sensation was sharply limited to one large area which had no demonstrable neurological distribution. In many of the cases the aches came only on rainy or damp days, while others had the sensation continually and were relieved only when they had something else to distract their attention. Frequently when the pains were referred to the region of a joint it was diagnosed as being due to "chronic arthritis." This was the situation in 21.5 per cent of the cases who complained of aches and pains. Visceral pain was very infrequent.

These vague yet very real complaints appear to have no common bases. Douthwaite⁴ has suggested that the pains might be due to a stretching of the bloodvessels as could occur with the patient's increased activity, but in our series of cases no constant relation was

found to exist between the pains and motion. In practically all instances the pains were relieved by physiotherapy but this relief was only temporary.

It will be noted that while headaches (43.3 per cent), dizziness (40.3 per cent), and vague somatic pains (38.7 per cent) occurred in about the same frequency, dyspnea, which was the next most frequent symptom, occurred in but 27.7 per cent of the cases. Not only were [the first three symptoms found with essentially the same frequency, but they often occurred in the same individuals (see Table III).

TABLE III.—NUMBER OF CASES COMPLAINING OF HEADACHES, DIZZINESS AND PAINS, ALONE AND IN COMBINATION WITH EACH OTHER.

Symptom.	Number of cases.
Headaches	473
Dizziness	440
Aches and pains	422
Three above symptoms in one case	117
Headaches and dizziness	168
Headaches and pains	74
Dizziness and pains	53
Headaches alone	114
Dizziness alone	102
Pains alone	168

Dyspnea and nycturia form a second group of complaints which occurred in approximately the same number of cases. There were, however, 97 patients who complained of both symptoms.

Dyspnea on Exertion was recorded in 27.7 per cent of the 1090 cases without complications. In none of these instances did there appear to be enough evidence to justify a diagnosis of myocardial insufficiency. Table IV shows the number of cases in which there occurred combinations of the four symptoms, dyspnea, palpitation, cardiac pain and edema, frequently seen in cardiac failure. Fifty-nine per cent of the patients with dyspnea did not complain of any of these other three symptoms. Only two records showed a history of orthopnea, a symptom which was practically universal in those patients who were diagnosed to be suffering from myocardial damage.

Nycturia occurred in 25.9 per cent of the cases. This symptom may be caused by various conditions and it is often difficult to determine the etiology in any single instance. In some cases it was apparently a habit developed earlier in life, in other instances insomnia was probably the underlying cause. In most cases the etiology was unexplained but in none of these instances were signs of renal damage discovered.

"*Nervousness*" was a term used to denote a variety of closely related symptoms. It included a tendency to worry, to become easily upset, or to become excited over matters of little importance.

Patients with such difficulties were frequently introspective, tending to dwell at undue length on their complaints, or were unstable emotionally. This sort of condition was noted in 13.2 per cent of the cases.

Palpitation of the Heart. The frequency with which this complaint occurred in combination with other cardiac symptoms, has already been referred to (Table IV). There were 20 patients who complained of both palpitation and nervousness.

TABLE IV.—COMBINATIONS OF DYSPNEA, PALPITATION, CARDIAC PAIN AND EDEMA.

Symptom.	Number of cases.
Dyspnea (total)	302
Palpitation (total)	143
Cardiac pain (total)	58
Edema (total)	46
Dyspnea and palpitation	69
Dyspnea and cardiac pain	17
Dyspnea and edema	14
Dyspnea and more than one of the other symptoms	25

Tinnitus was a complaint which was very distressing to the patient. It was present in 11.8 per cent of the cases. It was usually bilateral. The sound was, as a rule, steady and continuous, less when the attention was distracted and more prominent at night or when the patient was quiet and resting. In 74.6 per cent of the cases with tinnitus the patients complained of either headache or dizziness (Table V).

TABLE V.—THE NUMBER OF CASES WITH TINNITUS ASSOCIATED WITH HEADACHES OR DIZZINESS.

Symptom.	Number of cases.
Tinnitus (total)	129
Tinnitus, headache and dizziness	47
Tinnitus and headache	26
Tinnitus and dizziness	23

Weakness. Under this heading is included both increased ease to fatigue and also a subjective sense of weakness or loss of muscular power, the latter usually being referred to the extremities, especially to the legs. These symptoms were seen in 11.6 per cent of the patients with high blood pressure. Schultz and Biehn² have determined the frequency with which such symptoms were referred to various parts of the body, but in our series of cases no attempt has been made to classify in detail the areas involved.

The symptoms "nervousness," palpitation of the heart, tinnitus and weakness (Table II) occurred with apparently equal frequency. Other symptoms were recorded in no more than 5.6 per cent of the cases. Nevertheless, several of them deserve special mention.

Epistaxis has received considerable emphasis in the literature. It was noted in but 5.6 per cent of the Boston City Hospital cases. Paullin, Bowcock and Wood³ found it in 3 per cent of their series, while 39 of the patients reported by Douthwaite⁴ complained of hemorrhages from various parts of the body.

Despite the comparative infrequency of epistaxis, it possesses striking characteristics which show that it is an important sign. In 14.8 per cent of the patients who complained of nasal hemorrhage this was the sole complaint. In a great many instances the bleeding took place in the morning as the patient was rising from bed and in many others the epistaxis was brought on by exercise or emotion.

The bleeding rarely yielded to simple measures applied by the patient; cauterization was frequently of no avail, and repeated packings were often resorted to before the flow of blood was stopped. Probably hemorrhage from other parts of the body have the same etiological basis but these were very rare occurrences. Hemoptysis of unknown etiology was seen in 6 cases and there were two instances of unexplained rectal bleeding.

Numbness and Tingling. This type of sensation occurred in 4.4 per cent of the patients, and probably should be classed as a variation of the symptom discussed as "aches and pains." One-third of the cases with numbness and tingling also complained of vague generalized pains. In some cases this symptom was so prominent as to suggest combined system degeneration of the spinal cord, but such a diagnosis was never substantiated.

Edema (4.2 per cent) was never marked. It consisted usually of a slight swelling of the ankles noticeable toward the end of the day. The occurrence of this symptom was usually ascertained only after questioning the patient specifically. *Hot flashes* (2.2 per cent) occurred in 2 men and 22 women. In the women the menopause period had been passed through many years previously. *Cramps* (1.6 per cent) were confined to the legs, especially the calves, and occurred most frequently at night. Under the term *Angiospasm* (0.8 per cent) are included temporary paralyses, aphonias, and the like, which cleared up a few days after their onset and left no residual signs or symptoms. There were 7 patients (0.6 per cent) who complained of a *throbbing* sensation in various parts of the body other than the head.

It is difficult to determine the time of onset of these relatively rare complaints for the majority developed so gradually that a definite history of onset was not obtainable. In Table VI the complaints of the 156 (14.3 per cent) monosymptomatic cases are tabulated, and these probably represent the early symptomatology. It will be seen that pain of some sort was complained of in almost one-half of the cases.

There were 129 patients with hypertension who had no symptoms whatsoever. These cases were discovered among patients who came

to the medical outpatient department for routine physical examination or because of some disorder not related to the circulatory or renal systems. No relationship could be found between the height of the blood pressure and the severity, number or type of complaints. Several patients with blood pressures above 250 mm. Hg. had no symptoms whatsoever. Many patients showed fluctuations in the degree of hypertension without a corresponding variation in the severity of their complaints.

TABLE VI.—COMPLAINTS OF 156 MONOSYMPTOMATIC CASES OF HYPERTENSION.

Symptom.	Number of cases.	Per cent of 156.
Aches and pains	66	42.4
Headache	19	12.2
Dizziness	17	10.9
Nycturia	14	9.0
Dyspnea	9	5.8
Epistaxis	9	5.8
Palpitation	7	4.5
Tinnitus	4	2.6
Insomnia	4	2.6
Numbness and tingling	4	2.6
Weakness	2	1.3
Nervousness	1	0.6

The frequency of symptoms (Table II) is no indication of the subjective distress of the individual. Angiospasm, fainting and epistaxis, which were relatively rare occurrences, caused the patients more discomfort and worry than did the other symptoms. Aches and pain, dizziness, tinnitus and insomnia were also very troublesome while the remaining symptoms caused comparatively little distress.

The Complaints of Patients With Conditions Related to Hypertension. The presentation of the symptomatology of hypertension cannot be considered complete until an attempt is made to answer three questions. First, are symptoms specific for hypertension? Second, is the symptomatology due to the elevated blood pressure or is it the expression of some underlying condition which may or may not be related to the development of the high arterial tension? Third, is there any specificity in the symptoms exhibited by patients with hypertension? In order to answer these questions an analysis was made of the clinical histories of patients diagnosed as suffering from the following six conditions: chronic constipation, obesity, hypertrophic arthritis, menopause, menopause hypertension and psychoneurosis. These conditions were responsible for all the complaints and physical findings of the patients.

Chronic Constipation was chosen because, like hypertension, it represents a common condition found in individuals who tend to be mild chronic invalids. The symptomatology listed in Table VII is based on a study of the records of 96 consecutive cases of uncompli-

TABLE VII.—SYMPTOMS WITH AN INCIDENCE OF MORE THAN 10 PER CENT OCCURRING IN GROUPS OF PATIENTS WITH CHRONIC CONSTIPATION, OBESITY, CHRONIC HYPERTROPHIC ARTHRITIS, PSYCHONEUROSIS, MENOPAUSE WITH NORMAL BLOOD PRESSURE AND MENOPAUSE WITH HYPERTENSION.

Chronic constipation (96 cases).		Obesity (95 cases).		Hypertrophic arthritis (59 cases).		Psychoneuritis (120 cases).		Menopause with normal blood pressure (213 cases).		Menopause with hypertension (96 cases).	
Symptoms.	Per- cent- age fre- quency.	Symptoms.	Per- cent- age fre- quency.	Symptoms.	Per- cent- age fre- quency.	Symptoms.	Per- cent- age fre- quency.	Symptoms.	Per- cent- age fre- quency.	Symptoms.	Per- cent- age fre- quency.
Abdominal pain	52.1	Aches and pains	46.3	Aches and pains	98.3	Aches and pains	39.1	Aches and pains	48.8	Headache	53.1
Headache	33.5	Dyspnea	29.5	Nycturia	16.9	Headaches	34.1	Hot flashes	43.7	Dizziness	46.8
Gas (belching or flatulence)	26.1	Headache	26.3	Dyspnea	11.9	Dizziness	26.6	Headaches	38.0	Aches and pains	44.7
Nausea	22.9	Dizziness	13.7	Headache	11.9	Nervousness	24.1	Dizziness	33.8	Hot flashes	43.7
Dyspnea	19.8	Edema	11.6			Dyspnea	21.6	Nervousness	31.9	Dyspnea	27.1
Aches and pains	18.8	Nycturia	10.5			Palpitation	15.8	Dyspnea	24.4	Nycturia	21.9
Dizziness	16.7					Weakness	15.0	Nycturia	18.3	Nervousness	16.6
Palpitation	13.5					Nycturia	11.7	Weakness	16.5	Tinnitus	14.6
Abd. distention	12.5					Insomnia	10.8	Palpitation	13.6	Weakness	13.5
								Insomnia	10.3	Palpitation	11.5

cated chronic constipation with normal blood pressure. In general the symptomatology of chronic constipation was totally unlike that of hypertension.

Obesity. The typical patient with high blood pressure often is described as being overweight, if not actually obese. For this reason, the symptomatology of 95 consecutive patients with normal blood pressures who were suffering from no other condition save obesity, was determined. The results are presented in Table VII.

These patients complained of pains and dyspnea about as frequently as did those with hypertension.

Chronic Hypertrophic Arthritis. The symptomatology of this condition is presented in Table VII. The 59 case records examined represent only uncomplicated cases with normal blood pressures. Aches and pains were practically universal complaints but these pains were almost always (70 per cent) sharply limited to the region of the joints and rarely radiated or migrated to other parts of the body as was the case in patients with hypertension. In addition 50 per cent of the cases with arthritis showed the pains to be definitely related to motion. The remaining symptoms are similar to those seen in cases of high blood pressure but they were relatively infrequent complaints.

Menopause and Menopause Hypertension. During forty-two months, there were treated in the medical outpatient department 96 women who were diagnosed as in the menopause period and who were discovered to have hypertension. During the same period of time there were 213 women with normal blood pressures who were treated because of symptoms believed to be due to the menopause. The symptomatology of menopause hypertension (Table VII) is essentially the same as that of uncomplicated hypertension (Table II). The outstanding difference is in the frequency with which patients complain of hot flashes.

The symptomatology of uncomplicated menopause (Table VII) shows some differences from menopause associated with hypertension. Nervousness and insomnia occurred more frequently in women with normal blood pressures than in women with hypertension; tinnitus, on the other hand, was a less frequent complaint. Despite these differences, the individual case histories of menopause, menopause hypertension and uncomplicated hypertension are frequently indistinguishable from each other. It was not uncommon to discover a patient with normal blood pressure, having symptoms attributed to menopause, who later developed hypertension and who showed no change in symptomatology. There were an equal number of cases with both menopause and hypertension whose symptomatology persisted despite a subsequent diminution in the arterial tension to a normal level.

Psychoneurosis is another condition the symptomatology of which is similar in many respects to that of hypertension. The

points of difference between the two conditions are as follows: in 30.8 per cent of 120 consecutive cases of uncomplicated psychoneurosis, with normal blood pressure, there was discovered an underlying psychic conflict which may have been the basis for the condition. Both headaches and dizziness were frequent complaints but they occurred together only two-thirds as frequently as they did in hypertensive patients. Nervousness, insomnia, gastrointestinal complaints and numbness and tingling were found more frequently among psychoneurotic than among hypertensive patients, while nycturia and epistaxis were relatively infrequent symptoms. In addition, there were a variety of unusual complaints which could not be explained on an organic basis. These included such symptoms as sex impotence, aphonia, and anesthesia. It is mainly on the basis of such complaints that histories of psychoneurotic patients can be separated from those of individuals with hypertension, and yet there are many individual records which are so similar that the differential diagnosis cannot be made without the sphygmomanometer.

Discussion. Headaches, dizziness, aches and pain, dyspnea and nycturia alone or in combination were by far the most frequent complaints of the patients with arterial hypertension. Epistaxis and migraine, in contrast to observations made by others, were noted rather rarely. Complaints identical to those observed in patients with hypertension were present in a large proportion of the patients with obesity, menopause and psychoneurosis whose blood pressure was normal. Vasomotor disturbances in patients with obesity, menopause and psychoneurosis are common. It is also recognized that in the early stage of hypertension considerable fluctuation in the systemic blood pressure occurs. This fluctuation in the blood pressure is an expression of the changes in the peripheral arteriocapillary system which is regulated by the vasomotor center.⁵ Even in the later stages of hypertension when the blood pressure becomes more fixed, the cerebral circulation may be disturbed because of the presence of an increased arteriolar resistance and hence disturbed capillary circulation. The vasomotor disturbances in the circulation are the common explanation for similar symptomatology in hypertension, obesity, menopause and psychoneurosis. The symptoms of patients suffering from arterial hypertension cannot, therefore, be considered as specific or characteristic. It is also questionable whether the high arterial tension in itself is responsible for the symptoms, because no relationship could be demonstrated between the height of blood pressure and the severity of the complaints. In a considerable number of patients greatly elevated blood pressure was present without symptoms.

In Table VIII the symptoms of hypertension are arranged according to their probable anatomic source. A number of symptoms are placed under more than one heading, because the etiology may be

multiple. The majority of symptoms are referable to the disturbance of the central nervous system. Some of them, as hot flashes, angiospasm, throbbing, are the direct results of vasomotor changes in the cerebral vessels, while others may result indirectly from the effect of the changed cerebral circulation on the functions of certain regions of the brain. It is of interest that all the complaints referable to the heart and kidneys, with the exception of hematuria, may also result from vasomotor disturbances of central origin.

TABLE VIII.—SYMPTOMATOLOGY OF HYPERTENSION ARRANGED ACCORDING TO POSSIBLE ETIOLOGY.

Cerebral.	Cardiac.	Renal.	Other vascular areas.
Headache	Dyspnea	Nycturia	Epistaxis
Dizziness	Palpitation	Edema	Muscular cramp
Aches and pains	Weakness	Hematuria	Hemoptysis
Dyspnea	Cardiac pain		Weakness
Nycturia	Edema		Aches and pains
Nervousness			
Palpitation			
Tinnitus			
Weakness			
Insomnia			
Precordial pain			
Numbness and tingling			
Vague ocular symptoms			
Hot flashes			
Nausea or vomiting			
Angiospasm			
Throbbing			
Fainting spells			

The similarity of symptoms in patients with arterial hypertension, menopause, obesity and psychoneurosis does not, *a priori*, justify the conclusion that menopause, obesity and psychoneurosis are in etiological relationship to arterial hypertension. Nevertheless, it is more than a coincidence that two of the three conditions, namely, menopause and obesity, are frequently associated with hypertension. The relationship between psychoneurosis and arterial hypertension is probably closer than is recognized at present. Psychic trauma and conflict, abnormal sensitivity of the psyche, as well as the constant strain of life, play most important rôles in the development of psychoneurosis. These factors probably are often responsible for the development of hypertension and therefore the elimination of these psychic conditions plays a primary rôle in the prevention and treatment of hypertension.

Summary and Conclusions. 1. An analysis of the complaints of 1090 ambulatory patients with primary (essential) hypertension indicates that the following symptoms are present in more than 20 per cent of the cases: headache (43.3 per cent), dizziness (40.3 per cent), "aches and pains" (38.7 per cent), dyspnea (27.7 per cent), nycturia (25.9 per cent).

2. Epistaxis and migraine were infrequent symptoms.

3. Arterial hypertension is not associated with characteristic symptomatology. Almost all the symptoms of patients with arterial hypertension are referable to a disturbance of the central nervous system and are expressions of a disordered vasomotor system.

4. Among conditions with normal blood pressure, menopause, obesity and psychoneurosis showed symptoms similar to those of arterial hypertension. All four conditions frequently exhibit vasomotor instability.

5. Psychic conditions may play a more important rôle in hypertension than is realized, and therefore should be considered in treating the disease.

REFERENCES.

1. Kauffmann, F.: Ueber die Häufigkeit einzelner wichtigerer Klagen und anamnestischer Angaben bei Kranken mit arterieller Hypertension, München. Med. Wehnschr., 1924, 71, 1230.
2. Schultz, J. H., and Biehn, W.: Ueber die Häufigkeit einzelner wichtigerer Klagen und anamnestischer Angaben bei Kranken mit arterieller Hypertension, Deutsch. Med. Wehnschr., 1925, 51, 25.
3. Paullin, J. E., Bowcock, H. M., Wood, R. H.: Complications of Hypertension, Am. Heart J., 1926-1927, 2, 613.
4. Douthwaite, A. H.: Hyperpiesia, Guy's Hosp. Rep., 1928, 78, 59.
5. Weiss, Soma, and Ellis, L. B.: The Quantitative Aspects and Dynamics of Circulation in Hypertension, Am. Heart J., (in press.)
6. Weiss, Soma: The Nature and Management of Cerebral Hemiplegia in Patients with Arterial Hypertension, Med. Clin. North America, 1929, 13, 111.

VISCEROPTOSIS: ITS CLINICAL SIGNIFICANCE AND TREATMENT.

BY EDWARD L. BORTZ, M.D.,

THE LANKENAU HOSPITAL MEDICAL CLINIC, PHILADELPHIA, PA.

IN 1885 Franz Glénard first described the condition now known as visceroptosis. Since that time numerous articles by Rovsing,¹ Goldthwait,² Coffey,³ Martini,⁴ Mills⁵ and others have appeared in the literature emphasizing the importance and various phases of this condition. Following the epochal discovery of the Roentgen ray by Wilhelm Roentgen in 1893 with its subsequent usefulness in examination of the gastrointestinal tract, conceptions of the normal position which abdominal viscera occupy have been broadened. Anatomists described the position of organs with the subject in the supine state. Variability in size, shape and location appears to be the rule rather than the exception, especially with the relatively movable gastrointestinal tract. In 1923 Moody, van Nys and Chamberlain⁶ studied 300 men and 300 women, all presumably normal, taking Roentgen rays with the subjects in the upright posture. They concluded that the normal position of the stomach is lower than generally believed and that the term "gastroptosis" is

seldom justifiable. Practically all observers are agreed that the stomach and colon occupy a lower position in the female than in the male due to inferior musculature and ligamentous support. Before we label any position abnormal it is necessary to know the normal variations. Chamberlain⁶ and his associates found the greater gastric curvature 1 inch below the interiliac line in 4 per cent of male and in 10 per cent of female patients. We may look upon variation from two different angles.

There is constitutional variation, that is to say, a long stomach is the rule in a long body. The stomach fits the individual, so to speak; there is, also, individual variability. In either type stretching, elongation, relaxation, dilatation, or fixation by adhesions may develop. It is in this latter class that clinical symptoms may occur. The well-being of the individual is dependent to a considerable degree upon the integrity and proper function of the abdominal viscera. The gastrointestinal tract holds a large proportion of the blood. French authors have termed it the "coeur abdominal." Any marked distention, drag, relaxation or other alteration which interferes with the optimum function of this tract may have far-reaching effects on the individual.

The constitutional type known as "visceroptotic habitus," "maladie constitutionnelle" of the French, or "allgemeine Krankheit" of the Germans with malnutrition, narrow and flat thorax, acute costal angle, pot belly, hypotension and nervous disposition is common in all clinics and is easily recognized. These individuals frequently describe themselves as being "not sick or not well." Any one or all of their body systems are below par although complaints ordinarily point to either the gastrointestinal or cardiovascular tracts as the weakest links in the chain. Goldthwait² believes the condition is nearly always hereditary in these patients and maintains that the Mendelian law of inheritability of characteristics may be as true for the shape and position of the stomach as for the color of the eyes. Inheritance of a ptotic habitus renders the individual susceptible to a multitude of physiologic interruptions and aberrations which may give rise to a condition of chronic invalidism. These cases are easy to diagnose. Concerning their existence there is no controversy. Radiographic studies uniformly reveal a long, atonic stomach with its greater curvature deep in the pelvis. The colon, cecum, and one or both kidneys are likewise ordinarily in low position. It is improbable that the positions these organs assume would fall within normal variations.

In contradistinction to the class of patients just described, there exists a second large group in which no external factors lead one to suspect a disproportion between the body type and the shape and size of the stomach.

In a series of 100 cases studied in the Lankenau Hospital Medical Clinic we have interpreted the types as follows:

TABLE I.—TYPES OF VISCEROPTOSIS.

A. Congenital, 27 Cases.

1. Primary. Defect more pronounced and symptoms usually arise early in life.
2. Potential. Patients more nearly normal, that is, with better development of mesenteric supports. Symptoms may or may not arise, depending on resistance of individual and force of exciting circumstance.

B. Acquired, 73 Cases.

Secondary. Diseases, overwork. Repeated pregnancies, loss of weight, and so forth.

The age incidence and sex are shown in the following tables:

TABLE II.—AGE INCIDENCE.

Years.	No. cases.
10 to 20	4
20 to 30	32
30 to 40	16
40 to 50	24
50 to 60	20
60 to 70	4

TABLE III.—SEX.

	Female.		Male.
Single	22	Single	8
Married	46	Married	24

These patients offer an infinite variety of complaints.

In the series studied in the Lankenau Hospital Medical Clinic the majority of patients gave as their chief complaint some symptom referable to the upper or lower gastrointestinal tract; a smaller number presented symptoms pointing to the pelvis or lower spine. In the table below a complete analysis of the chief complaints offered by 100 cases, is presented.

TABLE IV.—ANALYSIS OF CHIEF COMPLAINTS IN 100 CASES.

	Per cent.		Per cent.
Gas	71	Pelvic distress	12
Constipation	63	Insomnia	12
Upper abdominal distress	49	Nausea and vomiting	12
General weakness	32	Dysmenorrhea	5
Swelling of stomach	30	Pain in chest	3
Nervousness	30	Diarrhea	3
Lower abdominal distress	28	Mucous stools	1
Backache	18	Bloody stools	1
Headache	15	Palpitation	1

Patients may or may not reveal disturbances of one or more of the major systems of the body. They are not of necessity undernourished, in fact, many are overweight, and Roentgen rays of the gastrointestinal tract are usually deemed unnecessary. If examined by Roentgen ray, the organs may be found in low position but the

prolapse may not be much beyond the extent of normal variation, that is to say, some point near the interiliac line. Tone is usually reduced.

It is chiefly this group of patients that has been studied intensively because the ordinarily prescribed modes of treatment have not given relief.

While a majority of the patients examined were found to be undernourished it is interesting to learn that 15 per cent were overweight. Focal infections are common in this class of patients, 26 per cent possessing a nidus somewhere in the sinuses, teeth, nose or throat. An unusually large proportion of patients in our group were found to have an erythrocyte count below 4 million.

It is worthy of note that 62 cases showed a diminished gastric acidity and 18 per cent exhibited an excess of acid in the gastric secretion.

Studies of the tonicity of the gastric musculature were made by Shoemaker. The basis of judgment of the gastric tonicity was the manner in which the stomach wall maintained a barium column of 500 cc. Hypertonicity was said to exist when the column was high and narrow; hypotonicity, when the lower half dilated and appeared flabby. The latter condition was found in 62 per cent of cases.

Lower bowel stasis is one of the most frequent accompaniments of visceroptosis. In our series 83 cases presented this sign.

TABLE V.—CHIEF PHYSICAL FINDINGS IN 100 CASES.

	Per cent.		Per cent.
Undernutrition	69	orthotonicity	33
Normal weight	16	hypertonicity	5
Overweight	15	Stasis	83
Focal infections (nose, tonsils, teeth)	26	Duodenal deformities	6
Anemia (below 4 million red blood cells)	40	Mobile cecum	82
Hypotension	22	Mucus in stool	10
Hypertension	12	Reduction of renal phenol-sulphonephthalein output below 40 per cent in two hours	8
Gastric hypoauidity	62	Relaxed pelvic floor	29
Gastric hyperacidity	18	Thyroid enlargement	19
Gastric musculature (by fluoroscope):		Arthritis	8
hypotonicity	62	Basal metabolism decrease	20
		(of 24 patients)	

Many were operated upon for appendicitis, cholecystitis, peptic ulcer, pelvic disease, intraabdominal bands or adhesions and other lesions.

TABLE VI.—OPERATIONS.

For.	No. cases.	For.	No. cases
Fibroid uterus—hysterectomy	2	Goiter	3
Chronic appendicitis	18	Varicose veins	1
Gastric ulcer	1	Tubo-ovarian disease	6
Duodenal ulcer	1	Herniorrhaphy	1
Pelvic operations (type not designated)	2	Nephrectomy	1
Cholecystitis	6	Hydrocele	1
Uterine suspension	2	Hemorrhoids	1

This table indicates the variety of operations performed on cases previous to knowledge of a ptotic bowel. Inattention to the latter condition explains, in many cases, incomplete postoperative recovery. If the lesion sought was found and removed, improvement but incomplete relief occurred. Infrequently the laparotomy was of no avail.

In surveying these cases one is forced to consider the possibility of ptosis of one or more intraabdominal organs as a contributing element to the patient's distress. It is comparatively rare to find a fallen liver or spleen, whereas, ptosis of the right kidney, the cecum and transverse colon is common.

TABLE VII.—ABDOMINAL ORGANS INVOLVED IN 100 CASES.

	Per cent.
Stomach	91
Transverse colon	88
Right kidney	3
Left kidney	1
Liver	2
Spleen	0

Additional lesions in the pelvis were present in the following proportions:

TABLE VIII.—CASES WITH ACCOMPANYING LESIONS OF PELVIS IN A SERIES OF 100 CASES.

	Per cent.
Uterine displacement	8
Lacerated cervix	32
Relaxed vaginal wall:	
(a) Cystocele	16
(b) Rectocele	2
Ovarian and tubal lesions	12

Ptosis frequently exists in association with the major diseases. Its presence may be the result of these lesions or may occur incidentally. In one patient with asthma, immediate and sustained relief from the asthma was obtained by correction of the visceroptosis.

TABLE IX.—ADDITIONAL DIAGNOSES IN A SERIES OF 100 CASES.

	Per cent.
Asthma	2
Hay fever	1
Pituitary dystrophy	1
Chronic pulmonary tuberculosis	2
Syphilis (Wassermann and Kahn 2, 3, or 4+)	10
Heart disease	8
Sciatica	11
Gastric ulcer	2
Duodenal ulcer	2
Pelvic disease	15
Chronic nephritis	7
Thyroid disease	5
Chronic cholecystitis	6
Mucus colitis	1

With the solid viscera and the transverse tube, displacement of the entire organs occurs. With the stomach a different condition arises. Its size, contour, and relative position depends on its contents, muscular tone and nerve integrity upon the presence or absence of gas, on the intraabdominal pressure, on the position, and contents of other organs, chiefly the large bowel, and on the body posture, osseous and muscular development and general nutrition. Since the stomach is fixed at the cardia and below the pylorus, it is obvious that prolapse of this viscus does not occur. Rather does it become elongated or dilated from lack of tone. The term "gastroptosis" is a misnomer. Gaston Lyon⁷ has suggested "vertical dislocation" while Martini and Comas⁴ propose "dolicogastrie" as a more correct designation. The latter term appears to fit the condition more suitably than others so far offered.

The opinions of twenty of the leading radiologists in four different countries were requested on the following five points:⁸

1. What, in your opinion, constitutes gastroptosis?
2. Is it important clinically?
3. Is it common?
4. When is, and when is not an elongated stomach ptosed?
5. To what are symptoms due, when present?

In answer to the question, "What constitutes gastroptosis?" the following impressions were given:

- (a) Prolapse of stomach as part of enteroptosis, only.
- (b) An organ which suggests drag on its attachments.
- (c) A relative elongation out of proportion to body habitus.
- (d) Greater curvature below left iliac crest.
- (e) Vertical elongation associated with atony and dilatation.
- (f) Pyloric sphincter appreciably below iliac crest.
- (g) Elongation of stomach with descent of distal third of greater curvature.

In response to the question concerning the clinical importance of gastroptosis, 4 men reported in the affirmative, 3 in the negative, and the others believed its importance was associated with that of enteroptosis from which symptoms due to gastroptosis alone could not be separated.

Eight of these radiologists look upon gastroptosis as a common condition and two regard it as uncommon. The remaining answers were evasive.

To the question "When is, and when is not an elongated stomach ptosed?" the majority conclude the diagnosis of ptosis can be made when the stomach length is out of proportion to the body type. One investigator states ptosis exists when the sphincter is below the iliac crest; another designates ptosis when greater curvature descends more than one-third the distance between the anterior iliac spine and symphysis pubis; the remaining observers held it to be a matter of personal opinion.

To the last question regarding cause of symptoms, these responses were given:

- (a) Drag on duodenum.
- (b) Tension.
- (c) Stasis.
- (d) Drag on mesentery with its resultant irritation to the sympathetic and vagus nerves.
- (e) Duodenal stasis with its resultant toxic absorption.
- (f) Compression on mesenteric artery.
- (g) Tension on bloodvessels, lymphatics, and to absence of support to the under surface of diaphragm.
- (h) Delay in emptying with gas and distention.
- (i) Mechanical interference plus disturbed gastric chemistry.

Developmental and Anatomic Considerations. Searching for the basis of signs and symptoms leads to a brief consideration of the embryology of the digestive tract and its supports. In the early stages of development the primitive gut is a straight tube. By an outpouching and elaboration of layers and glandular elements, the stomach is formed from the foregut. It is maintained in position chiefly by the mesenteric reflections, namely, the gastrophrenic and gastrohepatic ligaments and the continuation of the gut.

The entire large bowel develops from the caudal part of the primitive gut. By rotation and the formation of an inverted U anterior to the loops of the small intestine, the large bowel assumes its final position. The mesentery usually covers the anterolateral aspects of the rectum, sigmoid, descending colon and ascending colon, whereas, the transverse colon is entirely surrounded by peritoneum. Variations in these attachments explain many cases of mobile and prolapsed large bowel. Stable position and retention of viscera are not completed at birth. Victor⁹ has attempted to average the individual mesenteric variations and find an anatomic mean. Suffice to state that right here may be found certain important factors in the production of prolapse of the large bowel and cecum. Furthermore, there are five anatomic points which predispose to later kinking, mechanical obstruction or stasis, the foundation for troublesome constipation. These points are:

1. Near the left psoas at the pelvic brim.
2. Just proximal to the splenic flexure.
3. In the subpyloric region of the transverse colon.
4. Proximal to the hepatic flexure.
5. Cecum.

With full rotation and complete fusion of the mesentery it is impossible for ptosis to occur unless these attachments become weakened, then stretched. We know this takes place in cases of debilitating disease where loss of weight is the rule. This is acquired ptosis.

TABLE X.—IMPORTANT FACTORS IN PRODUCTION OF VISCEROPTOSIS.

1. Heredity.
2. Lack of exercise: Defective muscular development in childhood years.
3. Defective posture.
4. Embryonic defects of rotation and development. (Gastrointestinal tract.) (Mesenteric variations.)
5. Loss of weight.
6. Repeated pregnancies.
7. Debilitating diseases.
8. Overwork. Worry.
9. Lack of exercise: Overeating in adult years.
10. Weakening of abdominal wall by operation.

The abdominal cavity is spacious and roomy just beneath the diaphragm where the large viscera are found. Normally the lower ribs flare outward, the diaphragm arches upward, and the vertebral column has a gentle backward bow which curves forward at the lumbosacral level to produce, with the psoas muscles, a prominence or shelf on which the upper abdominal organs rest. The anterior muscles and aponeuroses complete the encasement.

The muscular osseous system or external sac, so-called by Bourcard¹⁰ incloses the digestive tube or internal sac. Between the two systems which may be conceived as acting in opposition, a condition of negative pressure is created. This pressure is an important adjunct in holding the organs in place and relieves the mesenterics of considerable strain:

1. Tonicity of abdominal wall.
2. Atmospheric pressure.
3. Extraperitoneal and mesenteric fatty tissue.
4. Tonicity of involuntary musculature of the gastrointestinal tract regulated by involuntary nervous system.
5. Fluid and solid contents of digestive tract.
6. Gaseous contents of digestive tract.

Thus a condition of intraabdominal equilibrium is established. Disturbance of this balance will tend to atony and dilatation of the digestive tract. Interference with circulation and pressure on involuntary nerves impairs the function of the viscera leading to poor alimentary hygiene, digestive disorders, constipation, etc. Faulty posture with relaxation of abdominal muscles, lowering of the anterior chest wall, loss of weight, for example, all tend to increase the intraabdominal negative pressure thereby placing a greater tension on the mesenteric attachments. Sagging of the large bowel with oftentimes a band or adhesion producing a constriction, the basis for excessive fermentation and therefore gas, dilatation and atony of the gastric wall with stretching and sagging set the stage for the clinical drama. If all of the organs descend, function may pre-

sumably continue without any major manifestations of impairment since their relative positions remain the same.

TABLE XI.—PROBABLE IMPORTANT FACTORS IN PRODUCTION OF SYMPTOMS.

1. Chronic obstruction.
2. Stasis.
3. Defective circulation of abdominal organs.
4. Pressure on involuntary nerves by sagging viscera.
5. Drag on common bile duct, portal vein, and hepatic artery.
6. Influence on secretion of digestive juices and ferments.
7. Pelvic pressure.

Usually mesenteric relaxation is not uniform, or, adhesions fix certain regions of the bowel in position while other portions prolapse. This is the basis for chronic obstruction with stasis and toxic absorption. Sir Arbuthnot Lane¹¹ has recommended colectomy for these cases pointing out that, by removal of a section of the large bowel toxic absorption is minimized. Sir Arthur Keith,¹² however, believes the stasis is due to dysfunction of the sympathetic nervous system. It is probable that both conditions play a part in causing stasis, stercoremia, and the clinical picture.

Differential Diagnosis. Visceroptosis clinically may resemble any abdominal condition in the acute or chronic stages. Many patients suffer from pain in the right upper quadrant. In the series here presented six individuals had had more than two attacks of typical biliary colic.

As seen in Table VI it is not infrequent that the patient has had a previous appendectomy with no relief.

Many German surgeons and radiologists note an intimacy between the occurrence of peptic ulcer and gastroptosis. Pelvic inflammatory disease is not infrequently present in ptotic patients. Goldthwait and others have found arthritis and rheumatic tendencies twice as frequent in patients with ptosis, as in nonptotic cases.

The difficulty in the diagnosis of ptosis is that it is too easy. So many patients have suffered for years from fallen organs and one often impatiently classifies them as "neurasthenic."

TABLE XII.—RESULTS OF TREATMENT IN 100 CASES.

	Per cent.
Improved	82
Unimproved	18

The treatment of no class of patients can produce more gratifying results or prompter relief than in this group. Though percentage of improved patients in our series may appear low, complicating conditions, as shown in Table XIII, may, in part, offer an explanation.

Unimproved cases in the series here presented, in certain individuals showed additional lesions (which in themselves may have been primary) as the following table shows:

TABLE XIII.—COMPLICATING FACTORS IN UNIMPROVED CASES OF 100 CASES STUDIED.

Chronic pulmonary tuberculosis	2 cases
Chronic heart disease	4 cases
Nephritis	3 cases
Thyroid disease	1 case
Pelvic disease (with adhesions)	5 cases

Treatment: 1. Prophylaxis.

2. Adequate care for coëxisting lesion, if present.

3. Removal of infective foci, chiefly in respiratory and pelvic tracts.

4. Elimination: Bowels, kidneys, skin, lungs.

5. Rest.

6. Diet.

7. Massage.

8. Exercise.

9. Abdominal support (belt, adhesive strapping, and so forth).

10. Medicine.

11. Surgery.

12. Advice about future precautions.

Goldthwait¹³ suggests attention to posture in school clinics as the proper prophylaxis for potential ptotic disorders.

The alleviation of symptoms requires treatment of a broad scope, suitable to the individual requirements of each patient. The time-consuming element in handling this large group of patients is in the search for the basis of the complaints. It takes time, occasionally doctors are impatient and the patient finally gravitates to the cults for relief.

By and large, the younger and more pliable the patient the more is to be expected from treatment. The utmost coöperation by the patient is likewise necessary. Institution of the proper therapeutic measures gives immediate relief in approximately 40 per cent of cases, but treatment, in order to be effective, must be followed over an extended period of time.

Treatment should aim to:

1. Return the organs to their normal position.

2. Improve the tone of the voluntary and involuntary nervous system.

3. Correct the posture.

4. Increase weight when necessary.

5. Inform the patient of the nature of the condition and outline precautions to avoid future disability.

In our experience less than 5 per cent of cases require hospitalization.

With the case thoroughly studied it is wise to explain to the patient in detail the nature of the condition and the rationale of treatment.

Hygienic measures including complete elimination through the bowels, kidneys, skin and lungs with rest of ten to twelve hours at night; two hours in the afternoon, and forty-five minutes lying on the left side after each meal to facilitate digestion and rest the mesenterics, are important. We prescribe a vigorous general massage twice daily using cocoa butter or oil of wintergreen.

Exercises directed to increasing the strength of the abdominal muscles, especially, and at the same time to raise the sunken chest and augment the diaphragmatic excursion are advised twice a day.

Foci of infection located usually in the teeth, tonsils, nares, sinuses, or pelvic tract are cleared up.

Diet is of primary importance. If the patient is suffering from an acute digestive rebellion it is wise to withhold all food for twenty-four to forty-eight hours. Frequent alkaline gastric lavage favors relaxation of the spasm and soothes the irritated mucosa. Fortunately this condition is not common.

Reflecting upon the nature of the stomach in these cases furnishes important information in outlining the diet. Four or five small meals are usually better tolerated than three large ones. As a rule it is prudent to administer fluids between meals. Immediately following ingestion patients should lie down, resting on the left side since this facilitates peristalsis and pyloric passage. The type of food is selected according to the needs of the individual. Obese patients should reduce and undernourished ones increase in weight.

The question of a mechanical support is one of the bugbears in the treatment of fallen viscera. Improper belts, improper adjustment of the correct type of belt, neglect to check up frequently by the fluoroscope, and, finally, permitting the patient to wear the support indefinitely, all add to, rather than alleviate, the discomfort. Probably no single therapeutic measure in the entire field of medicine has been so bungled as this of supports for ptosis cases. Not infrequently doctors have made the correct diagnosis but failed to lead the patient carefully over the correct road to relief.

Wearing a belt constantly has certain disadvantages. It is often uncomfortable and always is at first. It tends to weaken and destroy the strength of the abdominal muscles. Unless the advantages outweigh these possibilities the support is pernicious.

Innumerable corsets, binders, belts, stays, pads, supports and strappings have been tried.

About ten years ago Page constructed a support which consists of two connected vertical bars fitting over the sacrum with a stiff curved rod extending around either iliac crest, bent in such a way as to maintain in the suprapubic region a hard, oval leather pad. This has proven satisfactory. Each patient is fitted; then, following barium,

a check up is made with the fluoroscope. Not infrequently the transverse colon will slip down behind the pad unless the utmost precautions are followed. Once properly adjusted and the patient well informed concerning the manner in which it is put on while lying down, there should be a fluoroscopic check-up each week for one month and after that at monthly intervals. As soon as the tone and position of the stomach and colon are normal the belt should be replaced by a soft abdominal binder. Abdominal massage twice daily is advised to build up the abdominal muscles.

Numberless patients today are wearing belts which have outstayed their welcome.

Medicines to stimulate the appetite, to improve gastric secretion, and facilitate digestion are useful. Any of the tonics may be prescribed. In addition to these, atropin, following meals, is useful to assist in passage through the pylorus. We also routinely prescribe some combination of malt and cod-liver oil with orange juice. Oscodol has recently been tried with satisfactory results.

Neurotic patients often require a mild sedative during the early stages of treatment.

Less than 10 per cent of cases will require surgical intervention. Those with associated pathologic conditions of the stomach, biliary tract, bowel or pelvic region and, also, when thick adhesions hold the organs out of position, will not respond to conservative measures. It is important to keep in mind the indicated postoperative care these cases require.

With each patient informed of the nature of his condition and properly advised about the future, the chances for recurrence should be reduced.

In conclusion, we believe that the possibility of visceroptosis should be considered in each case that presents abdominal symptoms. Consider the vast number of persons who are below par, those who are neurasthenics, or chronic invalids. One wishes to dispel the thought. They are uninteresting. They are floaters from one doctor to another, from one hospital to another.

The medical profession does not appear to be impressed with the subject of visceroptosis. Patients submit daily to operations with the hope that they may be relieved. Investigation disposes one to conclude that, except for extraneous environmental and social problems of adaptability and compatibility, the greater proportion of these troublesome complainers are afflicted with some one or several of the stigmata designated as ptosis. This discussion attempts merely to focus the attention of the profession on the condition in the hope that more information may be obtained regarding the essential nature of the problem, and more satisfactory and efficient modes of treatment be revealed.

The distress of these patients is our problem. They deserve the best efforts of the best minds of our guild.

Summary. 1. Visceroptosis is a condition of downward displacement of the abdominal viscera that may exist in individuals who appear to be in perfect health.

2. The condition may be primary, that is, hereditary, or it may be acquired following somatic devastation from overwork, repeated pregnancies, prolonged disease, and so forth.

3. In a series of 100 cases studied in the Lankenau Hospital Medical Clinic the chief symptoms have been analyzed here. They usually pointed to the gastrointestinal tract.

4. Satisfactory therapeutic measures depend upon a consideration of the cause of the symptoms.

5. In the Lankenau Clinic a definite daily program is planned for each patient including proper diet, elimination, rest, massage, and when indicated, mild sedatives. All foci of infection are eradicated and, in selected cases, a Page abdominal support is applied. In a small percentage of cases requiring surgical intervention the fundamental rationale of the treatment should not be neglected.

BIBLIOGRAPHY.

1. Rovsing, Thor.: Gastrocoloptosis, *Ann. Surg.*, 1913, 57, 1.
2. Goldthwait, J. E.: An Anatomic and Mechanistic Conception of Disease, *Bost. Med. and Surg. J.*, 1915, 172, 881.
3. Coffey, R. C.: The Principles Underlying the Surgical Treatment of Gastrointestinal Stasis, Due to Causes Other than Strictural or Ulcerative Conditions, *Surg., Gynec. and Obst.*, 1912, 15, 365.
4. Martini, T.: Gastro-enterologic Pratique Dolichogastrie et Gastroptose (Leurs différences Cliniques et Radiologiques), *Bull. méd.*, Paris, 1927, 41, 901.
5. Mills, R. W.: Relation of Bodily Habitus to Visceral Form, Tonus and Motility, *Am. J. Roentgenol. (New series)*, 1917, 4, 155.
6. Moody, R. O., Van Nys, R. G., and Chamberlain, W. E.: Position of Stomach, Liver and Colon: Results of Roentgenologic Study in 600 Healthy Adults. Section on Gastro-enterology and Proctology, *J. Am. Med. Assn.*, 1923, 81, 1924. Cited by Rehfuess, in *Diseases of the Stomach*, Saunders, Philadelphia, 1927.
7. Lyon, Gaston: Le Houquet et son Traitement, *Bull. méd.*, 1927, 41, 901.
8. Personal communications.
9. Victor, A. C.: The Anatomic Basis for the Study of Splanchnoptosis, *Surg., Gynec. and Obstet.*, 1926, 43, 293.
10. Bourcard, L.: Étude Pathogénique du Déséquilibre Abdominal, *Paris méd.*, 1925, 57, 37.
11. Lane, Sir Arbuthnot: The Treatment of Non-malignant Affections of the Colon, *Brit. Med. J.*, 1922, xi, 1014.
12. Cited by Hugh Crouse in *Southwestern Medicine*; Type of Gastroptosis Demanding Surgery, April 11, 1927, 163.
13. Goldthwait, J. E.: Orthopedic Principles in the Treatment of Abdominal Visceroptosis and Chronic Intestinal Stasis, *Surg., Gynec. and Obst.*, 1913, 16, 587.

A TUMOR OF THE ADRENAL GLAND WITH FATAL HYPOGLYCEMIA.

BY HORACE B. ANDERSON, M.D.,

JOHNSTOWN, PA.

SHORTLY after the discovery of insulin by Banting and Best, the symptoms of hypoglycemia or hyperinsulinism became known to all physicians and many patients who used insulin. The symptoms

described then under the head of "insulin shock" or an overdose of insulin were weakness, nervousness, a "trembly feeling," slight confusion, rapid pulse, muscle twitching, profuse sweating, stupor, convulsions and coma. The severity of the symptoms, of course, was in direct proportion to the degree of hypoglycemia.

In 1924 Harris,¹ reasoning that various endocrine glands exhibited states of increased or diminished function, for example, the thyroid and pituitary glands, conceived the idea that the pancreas, theoretically at least, might under certain conditions show both a hypofunction and hyperfunction of its endocrine portion. Diabetes mellitus already having been thoroughly established as an example of hypoactivity of the islet cells, it only remained for him to find cases that demonstrated overactivity of the islet cells to substantiate his idea. Being on the lookout for such cases, he soon found some exhibiting symptoms of hypoglycemia; these, he thought, were due to overactivity of the islet cells and he gave the name hyperinsulinism to them. His cases gave symptoms of mild hypoglycemia which came on three to four hours after meals and were relieved by eating food. He believed, as does Jonas,² who gives an excellent review of the literature on hypoglycemia, that when the blood sugar dropped below 0.07 per cent symptoms of hypoglycemia manifest themselves.

While, no doubt, there are some cases of hypoglycemia accompanied by hypoglycemic symptoms due solely to hyperfunction of the island cells, all cases of hypoglycemia are not so easily explained; for, as Harris has pointed out, it also seems probable that disorders of the islet cells may be associated with dysfunction of the thyroid, the pituitary bodies, the adrenals and other organs of internal secretion.

Hartman,³ in a recent review of hypoglycemia, in addition to the endocrine dysfunctions, mentions progressive muscular atrophy, acute yellow atrophy of the liver, extreme physical action and tumors of the pancreas as additional causes for hypoglycemia.

Nor is the problem concerning the cause of hypoglycemia so simple as it may seem theoretically, as pointed out by a recent editorial writer:⁴ "The primary factors responsible for the change in the blood-sugar level may be either failure of the liver activities in liberating sugar or overfunction of the pancreas." It is a well-known fact that extracts from the pituitary bodies and adrenals play a part in mobilizing blood sugar. Although many German writers regard hypoglycemia an important feature in Addison's disease, and although Snell and Rowntree⁵ state they have noticed it in a few of their cases as a terminal phenomenon, the latter authors agree with Rosenow and Jogrettis that it is not a pathognomonic sign, nor even constant in its occurrence.

Stewart,⁶ in intensive studies on the function of the adrenals, found a low blood sugar only as a terminal factor in cases where

the cortex of the gland was destroyed. A further interesting observation which Stewart made and one that might have some bearing on the case herein reported was that when the cortex of the adrenals was destroyed the postmortem findings showed in practically every case marked hyperemia of the pancreas. Mochling's⁷ experiments led him to the conclusion that aplastic states of the pituitary gland are concomitant with aplasia of the suprarenal cortex and conversely, hyperplasia of the pituitary gland results in hyperplasia of the suprarenal cortex. Mochling's findings may also have a possible bearing on the present case.

Recently there have been reported a number of very interesting cases of hyperinsulinism or hypoglycemia due either to simple or overactivity of the islet cells, as in the case of Finney and Finney⁸ and in Case 2 of Allen's;⁹ or to overactive islet cells accompanied by tumors of the islet cells as in the following four cases:

The first case was reported by Wilder, Power and Robertson.¹⁰ A patient, aged forty years, three years prior to admission, showed some sugar in the urine. Symptoms had been present characterized by sudden attacks of faintness and weakness, numbness of the tongue and lips for eighteen months. For the past few months they had been more frequent and more severe. Profuse sweating and trembling have also been present. Eating and sweet drinks prevented attacks. Body weight dropped from 170 to 117 pounds. Intravenous glucose caused the blood sugar to rise in one-half hour from 85 to 218 mg. and traces of sugar were found in the urine. Three hours later the blood sugar dropped 131 mg. Epinephrin did not produce any effect toward mobilizing the blood sugar; neither did the pituitary gland extract. Twenty grams of glucose per hour were necessary to keep the blood sugar normal. Carcinoma of the tail of the pancreas was found at autopsy, and metastases to the liver. Carcinoma arose from the island cells of the pancreas.

The second case was reported by Thalheimer and Murphy.¹¹ A white woman, aged fifty-seven years, about two and a half years before admission, had attacks characterized by somnolence, restlessness and irritability. These attacks varied from two weeks to two months at first, but during the last year averaged about three a week. Epileptiform convulsions were present during the latter attacks. Autopsy disclosed pancreas of normal size except there was a tumor nodule, $1\frac{1}{2}$ to 1 cm., located in the tail of the pancreas, and on microscopic examination diagnosed as a tumor of the island cells, probably carcinoma.

McClenahan and Norris¹² reported the third case. A colored male, aged forty-one years, had attacks of loss of memory, lasting from one to one and a half hours. They could be prevented by eating. Symptoms had been present six to eight months. Provisional diagnosis of encephalitis. Spinal fluid, 20 mg. sugar per 100 cc. spinal fluid; blood sugar, 40 mg. per 100 cc. blood. Patient died of

bronchial pneumonia forty-eight hours after admission to the hospital. Blood sugar remained low in spite of glucose intravenously. Autopsy revealed generalized arteriosclerosis. Examination of the brain showed cerebral irritation manifested in the form of slight perivascular round-cell accumulations. The pancreas showed a tumor, measuring 15 by 7 by 16 mm., located at the junction of the middle and distal thirds. Diagnosis: Adenoma of islands of the pancreas.

The fourth case was studied by Howland, Campbell, Maltby and Robinson.¹³ In a case of dysinsulinism of six years' duration attacks of coma and convulsions, increasing in their frequency but warded off by the administration of food, were found to be caused by a low blood-sugar level. A study of the case revealed the erratic response to carbohydrate administration unless suitably administered and led to the diagnosis of this case as an islet-cell tumor of the pancreas. At operation a tumor of the pancreas was found and removed and a fruitless search for metastases was made. The patient recovered and has since been entirely free from the attacks. This constitutes the first successful treatment of such a case in the literature. The tumor was found to be a slow-growing carcinoma of the islet cells and insulin was recovered from the mass.

Warren¹⁴ has recently brought together 20 such tumors observed postmortem.

With this brief review of hypoglycemia, the writer wishes to report the following case of hypoglycemia associated with a tumor of the left adrenal gland and congestion of the tail of the pancreas and pituitary body. So far as he can determine, it is the first case of hypoglycemia of its kind.

Case Report. A white male, aged thirty-three years, married, having a wife and two children, was admitted to the Conemaugh Valley Memorial Hospital in a semiconscious condition. He had influenza ten years ago. Three months ago he had multiple small abscesses over the scalp which have disappeared and returned in successive crops up to the present time. He had treatment of these with a salve which the family thinks contained some lead. He also had an infection of the jaw twelve years ago. He denies any history of venereal infection. The family history is not important. The patient felt well and taught school on April 24, 1929, and went to bed that night feeling well. The following morning he could not be aroused except to answer questions. He remained in this semiconscious state until 7 P.M., when he became thoroughly conscious and seemed normal, except he could not remember that he had been ill and thought it was morning and wanted to go to school. He remained normal for two days, until 2 A.M., April 26, when he again became semiconscious and slightly delirious and remained so until admitted to the hospital the same afternoon.

A few days before the patient began to have semiconscious states as noted above his wife states that he complained at times of visual disturbances. There was no diplopia but rather a dimness of vision at times. This was most apparent when he drove to school in the mornings. He also complained of not being able to see things clearly when he awoke the day before admission.

Physical Examination. A young man of apparently thirty years of age, well nourished and well developed, lies quietly in bed, although respirations are moderately increased. With the exception of many small furuncles and scars over the scalp, the skin is clear. The general color of the skin is slightly cyanotic. The skin is moist and superficial capillaries are dilated. The patient is in moderately deep coma, but can be aroused sufficiently so that he will move his arms and legs and mutter incoherently if the supra-orbital nerves are pressed upon. The pupils are equal and react to light. There is a definite nystagmus present. There is no paralysis of the oculomotor nerves.

The teeth are in good repair; the tonsils are small; the throat is slightly congested but there is no acute inflammation. The ears are normal. There is no adenopathy. The thyroid gland is not appreciably enlarged.

The chest is well developed and normal to physical examination. The heart is normal in size and position and heart sounds are regular. Blood pressure was 120 systolic and 80 diastolic; pulse rate, 88; temperature, normal. The abdomen is negative, except for distention. The external genitalia are normal. Provisional diagnoses: Luetic meningitis, encephalitis, tuberculous meningitis, brain tumor, cerebral hemorrhage, brain abscess.

Clinical Course. Lumbar puncture produced clear fluid under normal pressure. At 6 P.M. respirations became irregular, pulse 120, with some rigidity of right arm. He was restless and perspired profusely. Chloral hydrate, sodium bromid and an enema were given. The following day he was still stuporous and restless and perspired profusely. In the afternoon 300 cc. of 20 per cent glucose solution was given intravenously. In half an hour the patient, aroused from his stupor, became conscious and took 6 ounces of orange juice with glucose. Later in the afternoon more orange juice and glucose were given.

On admission a Roentgen ray of the head was made and reported normal. The urine showed a heavy trace of albumin and a number of hyaline and granular casts, but nothing else of importance. The blood urea was normal. The spinal fluid was under normal pressure and presented a normal cell count and a negative Wassermann. An eye consultant stated that the fundi showed equal edema and venous congestion with chalky whiteness occupying the central position of each disk.

The patient rested quietly that night until 1 A.M. in the morning, when he became restless and semiconscious. During the early morning hours fruit juices were forced and he slept at intervals. He was clearer and quieter when morning came. Urine collected after intravenous glucose and fruit juices were given showed 10 per cent sugar. The blood count was 8000 leukocytes, 5,000,000 erythrocytes and showed a normal differential count. During the second and third hospital days the patient rested quietly and seemed improved, but at 2 A.M. in the morning of the fourth day he had a light convulsion and did not arouse from his sleep; but shortly afterward he became very restless and it became necessary to use a retention sheet. The body became rigid, the head retracted and he had an involuntary bowel movement. He sweated profusely and the lips and face became cyanotic. At 10 A.M. the patient was rigid, cyanotic, unconscious and sweating profusely. The pulse was irregular. A blood sugar showed 60 mg. per 100 cc. blood. Glucose by bowel was started and 300 cc. of 20 per glucose solution was given by vein. The patient's condition improved following glucose administration; but he remained semiconscious the remainder of the day and night. Eye consultant: "Retinal edema of right eye is greatly increased while left eye is much less. The chalky appearance is much greater of both disks and now resembles a complete nerve atrophy. The lesion is back of chiasm and to left central region." The

Wassermann and Kahn tests were negative and a second urine examination was reported normal.

On May 1, which was the patient's fifth hospital day, it became evident to the writer that, although the underlying disease process was obscure, the cause of this patient's symptoms was a hypoglycemia, and it further became evident that by giving sufficient glucose we could relieve these symptoms. So on the following days he was given an ample supply of carbohydrates. On several occasions in the early morning hours, when his carbohydrates ran low, he became restless and semiconscious and sweated profusely; but ample administration of glucose would relieve him.

Additional history on May 1 stated that four months previously, during a conversation at the home of one of his relatives, he paused in his conversation and was unable to talk for five minutes. Afterward he said he could think but could not express himself. About two weeks ago he had a short period in which he seemed to be irrational and said strange things. He has been rather listless and has had a tendency to become tired easily for six to eight weeks. It was also discovered that he saw double early in the present illness.

On May 3, his condition was much improved. He was rational, but thought came slowly. He had no headaches and no disturbance of vision.

The consulting neurologist reported: "When the man was first seen he was in deep stupor, not restless and free from motor excitement. There was a conjugated deviation to the left, but there seemed to be no (voluntary) eye muscle paralysis, as the eyes wandered about in all directions tending, however, to seek rest at the left. No pupillary irregularities. The mouth was drawn over to the right. Tongue movements not obtainable because of stupor. The eyegrounds appeared as follows: No edema; no papillitis; an ovoid area of shiny, glossy tissue at the region of the excavation, possibly an inflammation of the choroid more marked on the right. No evidence of increased intracranial tension.

The abdominal reflexes on the right were sluggish, on the left absent. Cremasterics normal. The limbs were all hypotonic. The reflexes in both upper extremities were normal. In the left leg there is a definitely positive Babinski, but a positive Gordon and Oppenheim. In both legs the patellar and Achilles reflexes are absent. It appears as if the man cannot voluntarily move any extremity; but the left arm and leg seem paralyzed, the right paretic. At the examination he could not be aroused from his stupor. He was incontinent. Sensation could not be tested on account of extreme stupor.

Today the picture has changed completely. The stupor is less marked; the man can be made to answer questions at times. There is singultus. The deviation of the eyes has disappeared, the facial paralysis has cleared up. The legs can be moved; the left Babinski is not elicited. (Oppenheim and Gordon still present.) There is obtained a history of slight personality changes two weeks ago. This recent psychosis, considered with the multiplicity of facial signs, and the fleeting nature of the signs, together with the objective findings enumerated above, lead to a diagnosis of subacute disseminated encephalitis.

On May 4 the patient is awake, talking and appears to be rational. He is rather restless, however, and his speech is slow and deliberate but not as marked as yesterday. He apparently has no visual disturbance. Stretches and sighs frequently as though he were very tired. No change in reflexes. Blood sugar, 157 mg. per 100 cc. of blood. On May 5 his condition was about the same, but he does not remember certain things that happened yesterday and did not remember certain visitors having been present. Eye examination shows fundi much clearer. Left eye has practically normal appearance except considerably central chalkiness of disk. Right eye vessels very tortuous with considerable hyperemia and chalkiness of disk.



FIG. 1.—The adrenal tumor with some normal adrenal tissue to the right. ($\times 14$.)

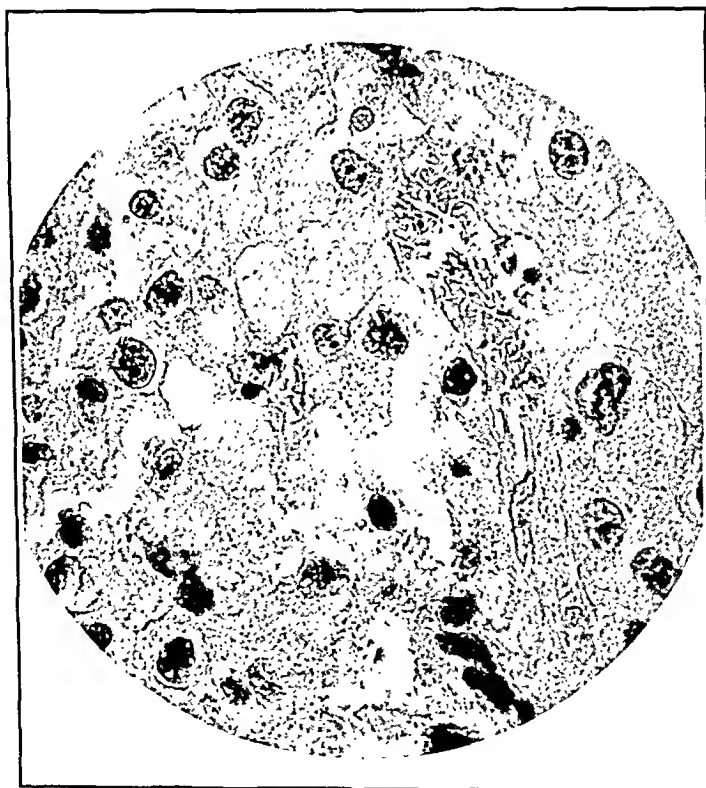


FIG. 2.—High power of the tumor, showing the general character and arrangement of cells. Note the relation to the capillary and the resemblance to adrenal cortical cells. ($\times 627$.)



FIG. 3.—Another area showing the variations in size and the tendency to giant-cell formation. ($\times 627$.)

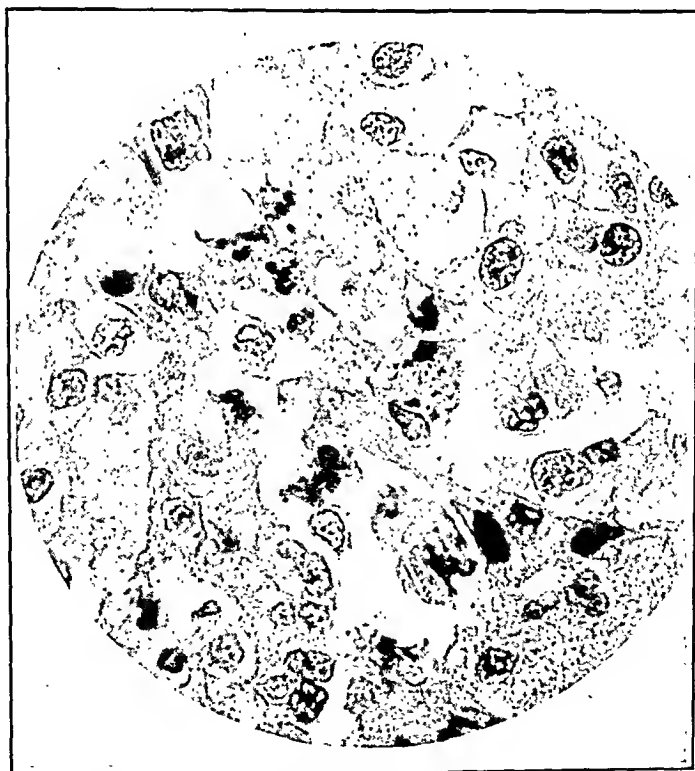


FIG. 4.—A rapidly growing area with tendency to cell degeneration. ($\times 627$.)

The engorgement is about one-half as much as on April 30, 1929. On May 6 the patient offers no complaints, but states that he "feels fine." This state of euphoria was frequently noticed during his convalescence. The blood sugar was 150 mg. per 100 cc. blood at that time. On May 18, after steadily improving, he was allowed to go home. The family was instructed to give him plenty of carbohydrates, especially when there were signs of weakness, sweating or a disturbance of his mental state.

Second Admission. The patient was readmitted, July 3, 1929, in a state of coma. He had been normal in every way for about three weeks and a half, when he became violent and would strike any person in sight. A week later this attack cleared up after the family was able to administer glucose. Two days before admission he became stuporous at 2 A.M., but came out of it at 6 P.M. The day before admission he went into another attack which he was still in when he was admitted to the hospital.

On readmission it was evident that the patient had lost considerable weight while at home. He was in light coma and every few minutes he became quite restless. The eyes showed a nystagmus. The skin was very moist and of a dull and slightly ashen color. The superficial capillaries seemed dilated, and there was moderate cyanosis. Respirations were between 20 and 30, the pulse 120 and the temperature 102° F. The blood sugar was 69 mg. per 100 cc. blood. The urine showed a light cloud of albumin, but no casts. The blood count was 5,000,000 red cells and 8000 white cells. The spinal puncture presented a normal fluid under normal pressure. The blood pressure was 95 systolic and 80 diastolic. He was slightly improved at times during the next few days, but even though he was given glucose by mouth and bowel and intravenously, he gradually grew worse and died, July 8, 1929. During the last few days of his life he presented a typical picture of insulin shock. The pulse grew weaker and became rapid. The blood pressure fell to where it could not be taken. He was in a profuse perspiration constantly and cyanosis increased. He died with edema of the lungs. Adrenalin, in doses of 1 cc. of a $\frac{1}{1000}$ solution, was given several times during the last two days that he lived, but apparently it had no effect.

Blood-sugar determinations during the second admission ranged from 60 to 80 mg. per 100 cc. blood.

Autopsy. The body is that of a fairly well-nourished and well-developed man, thirty or thirty-five years of age. Except for a furuncle on the chin and two small pustules on the scalp, the skin appears normal. The brain and meninges were found normal. The bloodvessels were congested and there was slight edema. Gross and microscopic sections made through important centers of the brain showed no lesions. Bloodvessels constituting the circle of Willis were not sclerotic. Pituitary body was definitely congested, but otherwise normal. Abdomen: The peritoneum was moist, transparent and glistening and the diaphragm was normal in position. The liver extended to the lower costal border on the right. Its size, color and consistency were normal. The spleen was slightly enlarged, but the capsule was smooth and the cut surfaces uniformly reddish-brown in color. The left adrenal gland was the site of an encapsulated globular mass which measured 8 cm. in diameter and weighed 400 gm. The surfaces were reddish in color and very vascular. The capsule was thin, but at places remnants of adrenal tissue could be detected. There were several prominent bloodvessels in or immediately beneath the capsule. The tumor mass, although lying immediately on top of the left kidney, was in no way attached to it. The right adrenal gland was smaller and more fibrous than expected. The kidneys were normal. The pancreas showed a definite increase in vascularity, especially that portion constituting the tail. The stomach and intestines did not show any gross lesions.

The chest was not opened in the usual manner, but the diaphragm was

opened and the lungs examined. No metastatic growths were found nor were there any signs of pneumonia. The mediastinum was normal. The heart was normal in size and position. The valves were not examined. The autopsy findings may be summed up as follows: A tumor of the left adrenal gland and congestion of the pituitary and congestion of the pancreas.

The microscopic examination of the tumor was interesting. Dr. James Ewing, after examining a section of the tumor, stated that to him it looked more like a liver-cell tumor than an adrenal tumor; but being an adrenal tumor, he thought it must be a medullary and not cortical growth. A cortical growth ought to have destroyed the whole adrenal. However, he states the cortical adrenal growths have very large cells like those of this tumor.

Dr. Shields Warren, after examining the tumor tissue, gave the following expression: "The tumor appears to be a carcinoma of the cortex of the adrenal gland. This is a fairly rapidly growing tumor with numerous giant cells and multiple mitoses. A striking feature is the large vacuoles in the nuclei of the tumor cells which give me the impression that they originally contained glycogen. Certain tumors do contain very large amounts of glycogen and are also known to produce either insulin or a substance very similar to it. This substance produced by tumors goes by the name of insuloid in the literature on the subject. Certain of the experimental rat tumors are known to produce considerable amounts of insulin-like substance."

Dr. H. E. Robertson express the belief that the tumor was a carcinoma of the adrenal cortex. He further states, however, that as far as he knows, hypoglycemia has not been observed in cases with tumors of this kind heretofore.

Comment. While it may be admitted that hypoglycemia is either due to hyperfunction of the islet cells or to disturbed liver function, it must also be admitted that disturbances in the functions of other glands may be important contributory factors in causing a pathologically low blood sugar. The writer will not attempt to explain the relationship between the hypoglycemia and the adrenal tumor in the case just reported, but does feel that if all such cases are carefully studied and recorded, in time, a satisfactory explanation can be made. Another advantage in reporting all such cases is this: We read them and are more likely to think of them when we see such cases in our practice, and thinking of them leads us to the proper diagnosis. A prompt diagnosis and good surgery in such cases may save lives as it did in the case reported by Howland¹³ and others. It is interesting to observe that in McClenahan and Norris'¹² case encephalitis was the provisional diagnosis; so it was in our case. They, however, found signs of perivascular round-cell infiltration in the brain which we did not find.

Summary. The case herein reported we feel is unique in that it is the only case we can find with typical symptoms of hypoglycemia

in which the only outstanding pathologic finding was a tumor of the left adrenal gland. There was also congestion of the pancreas and pituitary gland.

The symptoms were for a time relieved by glucose administration but later glucose failed to relieve the symptoms. Epinephrin was given one or two days before the patient died without effect. When the blood sugar fell below 0.07 the patient became restless, confused mentally and sweated profusely. The lowest blood sugar was 0.04 per cent.

REFERENCES.

1. Harris, S.: Hyperinsulinism and Dysinsulinism, J. Am. Med. Assn., 1924, 83, 729.
2. Jonas, L.: Hypoglycemia, Med. Clin. North America, 1924, 8, 949.
3. Hartman, F. I.: Med. Clin. North America, 1929, 12, 1035.
4. Editorial: Hyperinsulinism and Dysinsulinism, J. Am. Med. Assn., 1929, 93, 12.
5. Snell, M., and Rowntree L. R.: Clinical Experiences with Addison's Disease, Ann. Int. Med., 1929, 3, 6.
6. Stewart, G. M.: The Adrenal Glands, Arch. Int. Med., 1929, 43, 733.
7. Mochling, R. C.: The Pituitary Gland and Suprarenal Cortex, Arch. Int. Med., 1929, 44, 339.
8. Finney, J. M. T., and Finney, J. M. T., Jr.: Resection of Pancreas, Ann. Surg., 1928, 88, 584.
9. Allan, F. N.: Hyperinsulinism, Arch. Int. Med., 1929, 44, 65.
10. Wilder, M. M., Allan, F. N., Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of Pancreas; Hyperinsulinism and Hypoglycemia, J. Am. Med. Assn., 1927, 89, 349.
11. Thalhimer, W., and Murphy, F. D.: Carcinoma of Islands of Pancreas Hyperinsulinism and Hypoglycemia, J. Am. Med. Assn., 1928, 91, 89.
12. McClenahan, W. U., and Norris, G. W.: Adenoma of Islands of Langerhans with Associated Hypoglycemia, Am. J. Med. Sci., 1929, 177, 93.
13. Howland, G., Campbell, W. R., Maltby, E. J., and Robinson, W. D.: Convulsions and Coma Due to Islet-cell Tumor of Pancreas with Operation and Cure, J. Am. Med. Assn., 1929, 93, 674.
14. Warren, S.: Adenomas of Islands of Langerhans, Am. J. Path., 1926, 2, 335.

LIPOMA OF THE MEDIASTINUM.*

BY WALLACE M. YATER, A.B., M.D., M.S.,

FULL-TIME CLINICAL PROFESSOR OF MEDICINE AND CHIEF OF MEDICAL CLINICS,
GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE, WASHINGTON, D. C.,

AND

E. STUART LYDDANE, B.S., M.D.,

WASHINGTON, D. C.

(From the Georgetown University School of Medicine.)

LIPOMA of the mediastinum is very rare. Only 11 cases could be found recorded in the literature. In only 1 case, that of Lemon, was the diagnosis made prior to operation or necropsy. In 3 of the cases the tumor was removed successfully at operation. The

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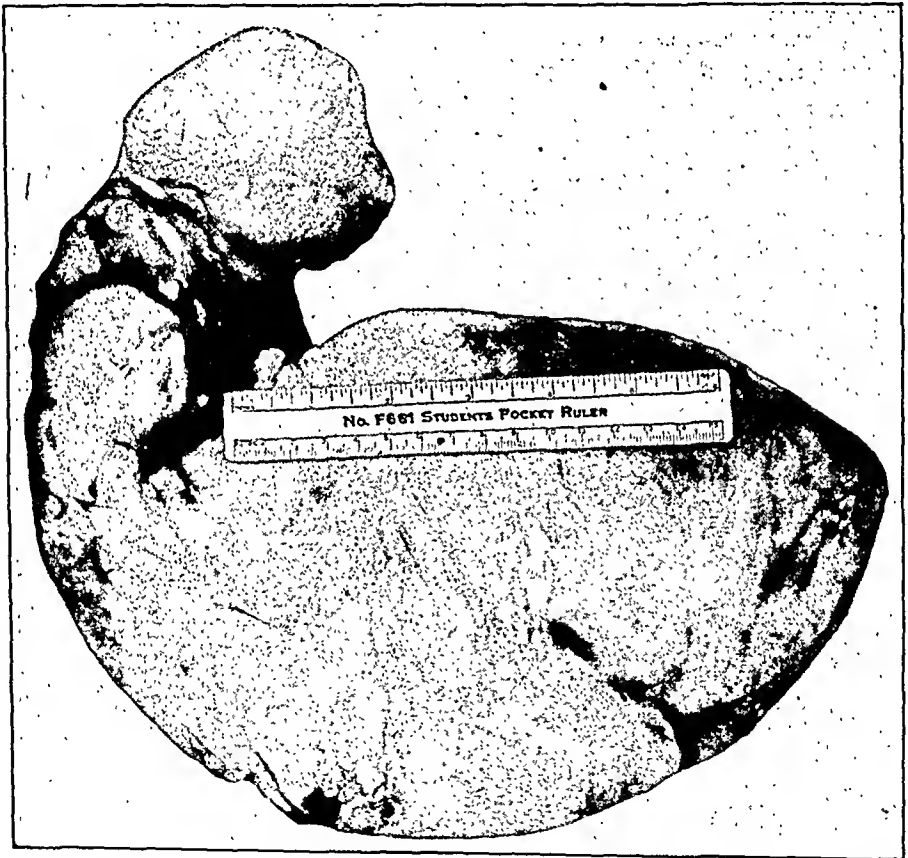
diagnosis was made in 2 instances after removal of a portion of the tumor which had forced its way through an intercostal space, and in another after removal of a small external tumor which was connected by a pedicle with the anterior mediastinum through a congenital aperture in the sternum. In the other 5 cases and in the 1 reported here the diagnosis was made at necropsy. The largest lipoma weighed 17 pounds and 6 ounces, and the smallest was about twice the size of a hen's egg. In 1 case the tumor was confined entirely to the anterior mediastinum. In 2 cases the tumor, relatively small, was situated in the superior mediastinum and projected into the neck, because of which location it was discovered in both instances. One or both pleural cavities contained part of the tumor in 6 cases. External tumors connected by pedicles with the internal lipoma through an intercostal space were present in 3 cases, and an external tumor connected by a pedicle with the internal tumor through a defect in the sternum in 1. In most instances the tumor was well encapsulated and easily shelled out. From the histologic examination only 2 of the tumors were diagnosed as congenital lipoma; the others which were examined were simple lipomas.

Well-marked symptoms due to pressure were noted in only 3 cases. Physical signs were recorded in 6. The accompanying table gives the salient data in the 11 cases previously reported and in the following case:

Case Report. A white man, aged forty-four years, entered Georgetown University Hospital on July 10, 1929, with the symptoms and signs of lobar pneumonia. He had had influenza in 1918 and claimed that ever since that time he had had some dyspnea on exertion. He had never missed a day at his vocation as a carpenter, and except for the mild dyspnea had been perfectly well. Two days before admission he had felt somewhat ill and soon developed a pain in the left lower chest anteriorly with cough and expectoration of a mucoid sputum which had become blood tinged. Examination on admission revealed a very robust man of good color, but evidently severely ill. He was groaning and dyspneic, with dilating *alae nasae*, and coughing rusty sputum. Crackling inspiratory râles were audible throughout both lungs, but there were no definite consolidations. There was flatness on percussion over the right lower chest with considerably diminished breath sounds. The cardiac sounds and blood pressure were normal. The abdomen was somewhat distended and tense, the tenseness being apparently due to enlargement of the liver. The temperature was 102° F., the pulse rate 100 and the respiratory rate 28. A Roentgen ray picture of the chest taken in bed with the portable machine revealed a dense opacity over the lower two-thirds of the right chest and an opacity also in the left chest corresponding to the lower part of the upper lobe. Examination of the sputum revealed pneumococcus Type IV. The hemoglobin was 79 per cent (Dare). The erythrocytes numbered 3,910,000 and the leukocytes 15,750 per c.mm. of blood, of which 87 per cent were polymorphonuclear neutrophils. The urinalysis showed a trace of albumin and a few leukocytes.

The patient's condition became progressively worse; the temperature rose to 105° F., the pulse to 146 and the respiratory rate to 30 a minute. Signs of involvement of the entire left lung developed. On the morning of the fourth day in the hospital the patient died.

Necropsy (Partial). On opening the thoracic cavity, a large light yellow tumor was seen to fill much of the right side of the thorax, the anterior mediastinum and to cover the pericardium. The mass was easily shelled out *en toto* and grossly appeared to be a lipoma. It was held in position by several layers of thin fascia and apparently originated from the fat in the superior mediastinum in the region of the thymus. The right lung was about one-third normal size and appeared normal. The entire left lung was completely consolidated and in the stage of red hepatization. The heart appeared normal but the pericardium was completely covered by a thick fold of the lipoma as before mentioned. The lipoma weighed $8\frac{1}{4}$ pounds, was relatively avascular and was nourished by two fairly large vessels. On section the tumor was seen to be a pure lipoma and was quite yellow (see illus.). Microscopic sections of the tumor showed that it was a pure lipoma.



Photograph of cut section of lipoma showing its lipomatous nature and its relative avascularity.

Comment. Lipoma of the mediastinum is not the only intra-thoracic lipoma. A fatty tumor may also originate from the endothoracic fascia, from the subpleural fatty tissue of the diaphragm or from the subperitoneal fat forcing its way through the fibers of the diaphragm. Rokitsky noted that subpleural fat along the intercostal spaces is often abundant and at times projects into the pleural cavity as notable lobulated masses. Chiari is stated to have

observed in an elderly female a pendulous lipoma the size of a walnut projecting into the pleural cavity from the seventh left rib. Czerny removed a lipoma the size of a man's head from beneath the left scapula of a boy, aged eighteen years, which passed by a ramification into the extrapleural space between the seventh and eighth ribs. In his inaugural dissertation Plettner described in an elderly woman a lipoma the size of a child's head which projected from the left wall of the thorax and was found to connect with a flattened subpleural lipoma the size of a hen's egg by a pedicle between the fourth and fifth ribs. Gussenbauer's oft-quoted case was that of a lipoma at the border of the left mammary gland of a woman, aged twenty-nine years, which was connected to an intrathoracic counterpart by a pedicle passing through the second intercostal space. Clark and Conner each reported a case of subpleural lipoma of the diaphragm, and Cruveilhier mentions the occurrence of fatty tumors of the diaphragm which have forced their way through the fibers of the diaphragm from the subperitoneal fat, at times accumulating behind the ensiform cartilage.

Whether the lipoma originates in the anterior mediastinum or from the endothoracic fascia, the various shapes it may assume and the direction it takes as it grows are interesting features. Why in some instances it breaks through an intercostal space at one point and expands external to the thoracic cage, while in others it may assume a much larger size but remain entirely within the chest, is difficult to explain. The pressure exerted by the heart action and that produced by the lungs during inspiration may be assumed to be sufficient to cause part of the tumor to break through a congenitally weak spot in an intercostal space. The case of Garnier and Grosjean illustrates these factors in a patient with a congenital defect of the sternum.

Summary. Lipoma of the mediastinum is very rare, only 12 cases including the one described in this report having been recorded as far as could be ascertained. In only 1 instance was the tumor confined to the mediastinum. In the others it had grown externally either upward into the neck or through an intercostal space or defect of the sternum to form a tumor of the chest wall, or it had forced its way into one or both sides of the thoracic cavity. Symptoms due to pressure were noted in only 4 cases. In the case reported here moderate dyspnea on exertion had been present for eleven years, and the patient died of lobar pneumonia. The lipoma weighed $8\frac{1}{4}$ pounds and filled the anterior mediastinum, the pericardium and the lower two-thirds of the right thoracic cavity.

BIBLIOGRAPHY.

- Beatson: A Fatty Tumor Removed from the Superior Mediastinum, *Glasgow Med. J.*, 1899, 51, 57.
 Bertoli, P.: Un raro caso di lipomi multiple sottopleurici nel mediastino anteriore, *Gazz. d. osp.*, 1908, 29, 1108.

SALIENT DATA OF THE TWELVE CASES OF LIPOMA OF THE MEDIASTINUM.

Case.	Author.	Year.	Sex.	Age at death.	Location.	Size and shape.	Operation.	Cause of death.	Character of tumor.	Symptoms and signs.
1	Cruveilhier ¹	1856	?	?	Anterior mediastinum and externally by pedicle	?	Removal of external portion	Suppurative inflammation of anterior mediastinum	Pure lipoma	Details not given.
2	Krönlein ²	1887	F.	1 yr.	Anterior mediastinum, most of left and part of right chest; externally by pedicle through third right intercostal space	Internal part, size of child's head	Removal of external portion	Bronchopneumonia and pleuritis	Congenital lipoma	Few symptoms or signs.
3	Bentson	1899	M.	45 yrs.	Superior mediastinum and above sternal notch	Orange	Removed successfully	Fatty lobules; no sections	No symptoms.
4	Garnier and Grosjean	1903	M.	56 yrs.	Anterior mediastinum and externally by pedicle through defect in sternum	External part walnut size	Removal of external portion	Pure lipoma	External tumor and pain for three months.
5	Fitz	1905	M.	34 yrs.	Anterior mediastinum and left thoracic cavity	Pear shaped; size of fetal head	None	Purulent pericarditis	Congenital because of hypoplasia of left lung	No symptoms.
6	Ewing	1905	M.	Middle age	Anterior mediastinum, lower half of left chest, ramifying in many directions	Five main lobules, each size of goose egg	None	Pneumonia of right lung	Lobules connected by broad pedicles; fetal fat tissue	No symptoms; physical signs of tumor.
7	Bertoli	1908	M.	57 yrs.	Left side of anterior mediastinum	Covered 8 sq. cm.	None	Empyema of right side	Lobules (12), numerous capillary sinuses and scattered monocytes	Dissecting room cadaver; no history.
8	Leopold	1920	M.	37 yrs.	Anterior mediastinum, right and left thoracic cavities	17 pounds, 6 ounces	None	Asphyxia	Large fat cells	No symptoms recorded.
9	Beyers	1923	M.	22 mos.	Anterior mediastinum and externally by pedicle through sixth left intercostal space	Each portion about 2 in. in diameter	Removed successfully	Pure lipoma; section not reported	Cough and dyspnea, 17 mos.; edema from below upward, 9 mos.; cyanosis of head and arms.
10	Lemon	1925	M.	48 yrs.	Anterior mediastinum and right thoracic cavity	Size of quart cup	None	Asphyxia	Pure lipoma; lobulated	No symptoms; external tumor noted for 12 mos.
11	Graham and Wiese	1928	M.	43 yrs.	Anterior mediastinum and supra-sternal	Twice size of hen's egg	Removed successfully	Pure lipoma	Pressure symptoms, 7 yrs.; cough, hemoptysis, dyspnea, cyanosis; physical signs of tumor.
12	Yater and Lyddane	1929	M.	44 yrs.	Anterior mediastinum, precordium and lower two-thirds of right thoracic cavity	8½ pounds	None	Lobar pneumonia, entire left lung	Pure lipoma	Choking spells, 6 mos.; pain in neck and right chest; cyanosis of finger tips at times; numbness of right arms and chest at times. Mild dyspnea, 11 yrs.

¹ Case of Morel-Lavallée.

Beyers, C. F.: A Case of "Subpleural" Lipoma in a Child, *Lancet*, 1923, 204, 283.

Chiari: Quoted by Gussenbauer.

Clark, F. W.: Subpleural Lipoma of the Diaphragm, *Trans. Path. Soc. London*, 1887, 38, 324.

Conner, L. A.: Lipoma of the Diaphragm, *Proc. New York Path. Soc.*, 1897-1898, p. 43.

Cruveilhier, J.: *Traité d'anatomie pathologique générale*, 1856, 3, 315.

Czerny: Exstirpation eines kopfgrossen, subpleuralen Lipoms, Tod durch septische Pleuritis, *Wien. med. Wchnschr.*, 1875, 25, 166.

Ewing: Discussion of Fitz' Case, *Trans. Assn. Am. Phys.*, 1905, 20, 66.

Fitz, R. H.: Intrapleural Lipoma; Acute Pericarditis; Pericardial Exploration, *Am. J. Med. Sci.*, 1905, 130, 785.

Garnier, C., and Grosjean, L.: Variété rare de lipome pédiculé' douloureux de la région sternale, *Rev. méd. de l'est*, 1903, 35, 654.

Graham, E. A., and Wiese, E. R.: Lipomas of the Mediastinum, *Arch. Surg.*, 1928, 16, 380.

Gussenbauer, C.: Ein Beitrag zur Kenntniss der Subpleuralen Lipome, *Arch. f. klin. Chir.*, 1892, 43, 322.

Krönlein, R. U.: Geschwulst des Mediastinum anticum, *Arch. f. klin. Chir.*, 1887, 21, Suppl., 157.

Lemon, W. S.: Lipoma of Mediastinum, *Med. Clin. North America*, 1925, 8, 1247.

Leopold, R. S.: A Case of Massive Lipoma of the Mediastinum, *Arch. Int. Med.*, 1920, 26, 274.

Morel-Lavallée: Quoted by Cruveilhier.

Plettner, G. A. L.: Beitrag z. Kenntniss der tiefgelegenen (Subfascialen) Lipome, Halle, 38 pp., 80, Leipzig, Bréitkoff u. Hartel, 1889.

Rokitansky: *Lehrb. d. path. Anat.*, 1861, 3, 39.

Vogt, C.: Quoted by Krönlein. Einige seltene congenitale Lipome, Berlin, Lange, 1876 (Thesis).

ALIMENTARY HYPERLIPEMIA.

A STUDY OF THE LIPEMIC CURVE.

BY DR. B. HEJDA,

PRAGUE, CZECHOSLOVAKIA.

Translated from the Czech by Henry J. John, M.D.

(From the Second Czech Clinic of Internal Medicine of Prof. J. Pelnar.)

UNDER normal conditions the amount of fats in the blood stream maintains a constant level and only during the postprandial period does it rise temporarily. It is interesting for the clinician to study the changes in this curve during alimentary hyperlipemia and its variations under abnormal conditions. It is more than probable that such a study may throw some light on the thus far unsolved problems pertaining to fat metabolism and it may even prove to be useful as a clinical method of investigation.

The technique for the determination of fats in the blood stream is complicated, a fact which no doubt has been the reason why thus far this method of investigation has not been widely used. Four years ago Vanysek studied this problem in our clinic. At that time we tried to determine the fat content by the use of Bang's method and determined the petroleum content of fatty acid and

cholesterin, but our results were not satisfactory; there remained to try other macromethods which in themselves were accurate, but were not available to us because of their great complexity and the impracticability of making serial observations. Bloor's method was finally chosen for our purpose.

I am, therefore, continuing the investigations for Vanysek,¹ who has reviewed the literature of fat metabolism in the human body.

That which we summarize under the general conception of lipemia is really a summary of metabolites which vary widely both chemically and physiologically and yet maintain their quantitative interrelationship (Terroin's *constance lipémique*). For example, if we burden the organism with neutral fats there is an increase in the blood content not only of the neutral fats but also of cholesterin. The other fatty bodies behave similarly. All the fats which are taken in as food lipoids are also present. Moreover we know that cholesterin is absorbed when it has been administered together with neutral fats, whereas pure cholesterin will pass out with the feces. It seems, therefore, that in the study of fat metabolism it is correct first of all to study lipemia.

Under normal conditions the fasting fat level, as determined by the method of Bloor, lies between 0.5 and 0.7 per cent. The fat is present in the blood stream as a fine emulsion. Under normal conditions the serum is clear and only when the fat content reaches above 1 per cent (according to Bloor) does the hyperlipemia appear as a milky discoloration. The only exception is the so-called masked hyperlipemia which accompanies the so-called retention icterus (Brulé), in which in spite of a high hyperlipemia the serum is clear; the cause for this is apparently the concentration in a fine state of emulsion.

After the ingestion of fat one can follow the course of hyperlipemia microscopically by the appearance of milky serum and, finally, by its disappearance (hemoconia). In the literature one finds that the fat level starts rising two hours or more after the absorption of ingested fat reaches the blood stream through the chylous channels and through the thoracic duct. Such a hyperlipemia reaches its highest point in about six hours and in from eight to ten hours the lipemia returns to its normal level. Bang has shown, however, that if we use smaller doses (from 20 to 50 gm. of butter) the curve is markedly shortened and reaches its maximum in three hours.

In this work, therefore, I have used as a test breakfast 50 gm. of butter given with one roll of bread and 0.25 liter of slightly sweetened coffee with cream. The lipemia estimations were made at intervals of one and a half hours. I found that under normal conditions the fat level at the end of one and a half hours was not changed, in three hours it was slightly raised, in four and a half hours the curve reached its maximum level and in six hours it returned to its original

value. The ratio of the maximum lipemia to the fasting lipemia averaged about 1.3. From these experiments we secured a certain type of curve which we could consider as normal in type and other curves that could be considered as pathologic variations.

Nineteen cases in which lipemia estimations have been made are summarized in Tables I to III and the lipemia curves in these cases are shown in the charts.

TABLE I.—NORMAL RELATION OF FASTING TO MAXIMUM LIPEMIA.

Case No.	Age.	Diagnosis.	Fasting lipemia, per cent.	Lipemia (per cent) after ingestion of fat.					Ratio of fasting to maximum lipemia.
				1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	7½ hrs.	
1	52	Mesaortitis luetica; aortic aneurysm	0.56	0.56	0.65	0.73	0.56	...	1.30
2	16	Acute anterior poliomyelitis	0.66	...	0.81	0.86	0.66	...	1.30
3	32	Trauma of spine; paraparesis of lower extremities	0.73	0.73	0.77	0.96	0.73	0.73	1.31
4½	44	Traumatic neurosis	0.60	...	0.65	0.81	0.60	...	1.35
5	18	Muscular atrophy	0.42	...	0.48	0.54	0.42	...	1.29
6	51	Gastritis; hypoacidity	0.54	...	0.58	0.69	0.54	...	1.28
7	27	Sine morbo	0.56	0.73	0.56	...	1.30

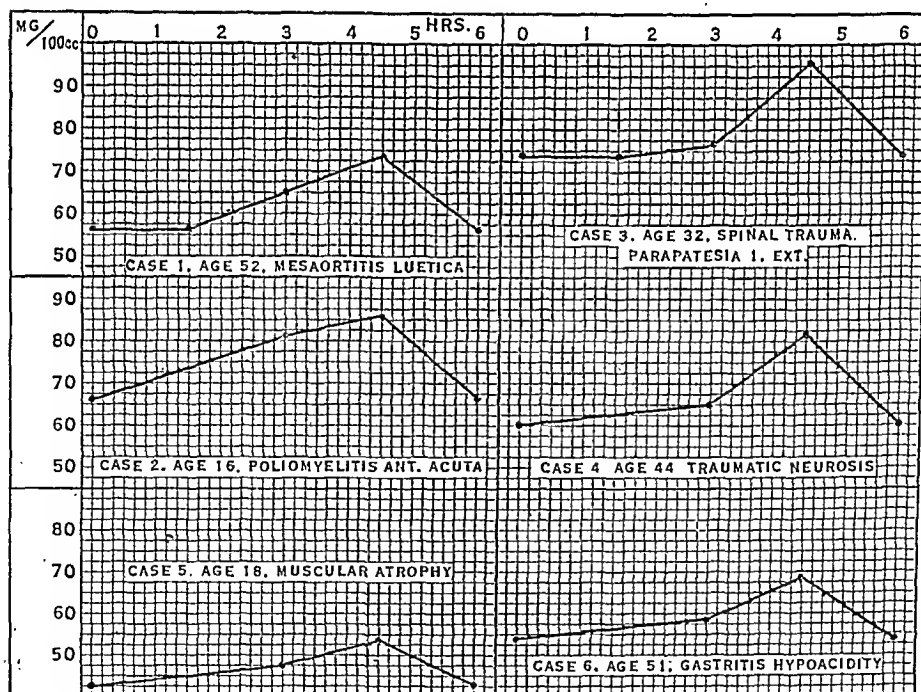


CHART I.

From the findings given in these tables we may conclude that only the first 7 (Table I) had a normal lipemia (the muscular-atrophy case alone has a markedly low-fasting lipemia). As was stated above,

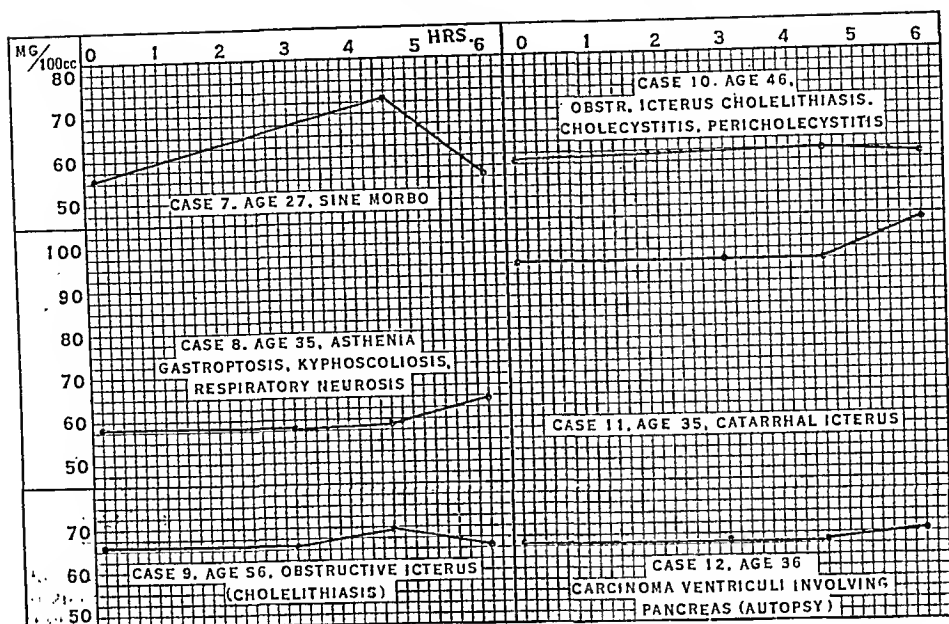


CHART II.

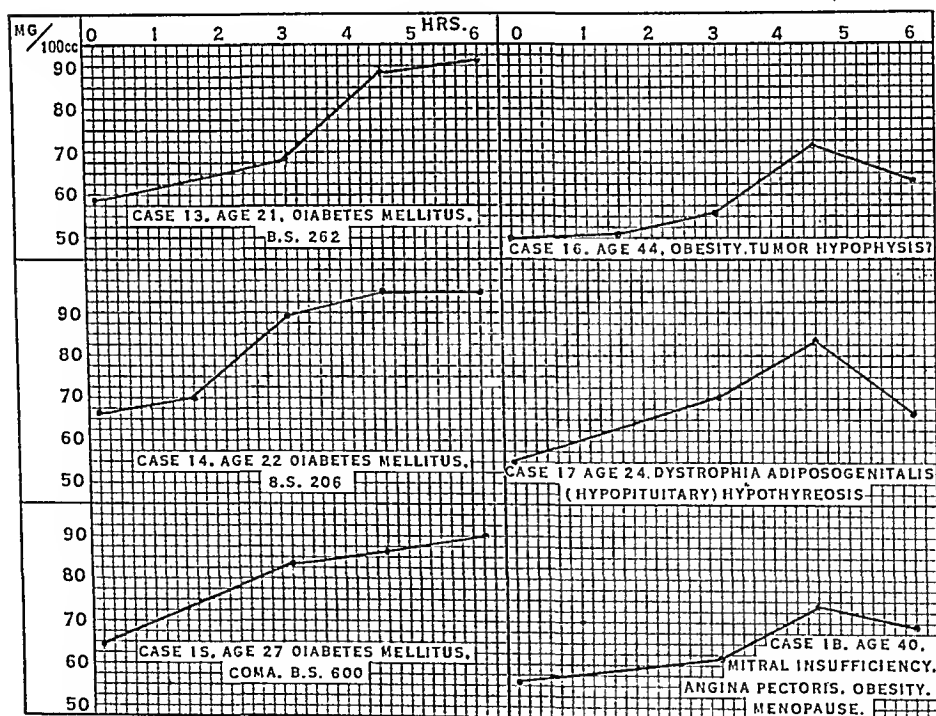


CHART III.

the hyperlipemia appears between the second and third hour after the ingestion of fat and reaches the maximum between the fourth and fifth hours, returning to its original value during the sixth hour. The normal lipemic ratio is between 1.27 and 1.35.

Cases 8 to 12 (Table II) form a second group; these are cases in which the absorption of fat from the gastrointestinal tract into the blood stream is delayed. Thus, for instance, in Case 8 the influence of gastric function on the curve is definitely shown; marked gastrop-tosis with atony and the slow evacuation results in a slow rise of the lipemia level at a time when normally the hyperlipemia is descending. Besides this general asthenia we must consider as well the asthenia of the pancreas. Cases 9, 10 and 11 are cases of mechanical icterus, of which only the last one had a latent fasting hyperlipemia. All 3 showed but a slight rise of the fat level in six hours. In the twelfth case of carcinoma of the stomach involving the pancreas, with resultant lowered pancreatic lipase, the lipemia did not change the first six hours and there was but an insignificant rise in the last hours.

TABLE II.—DELAYED ABSORPTION OF FAT FROM INTESTINE.

Case No.	Age	Diagnosis.	Fasting lipemia, per cent.	Lipemia (per cent) after ingestion of fat.			Ratio of fasting to maximum lipemia.
				3 hrs.	4½ hrs.	6 hrs.	
8	35	Asthenia; gastrop-tosis; kyphoscoliosis; respiratory neurosis ¹	0.58	0.58	0.59	0.65	1.12
9	56	Obstructive icterus (cholelithiasis) ²	0.66	0.66	0.69	0.66	1.05
10	46	Obstructive icterus (cholelithiasis); cholecystitis; purulent pericholecystitis ³	0.58	...	0.60	0.59	1.03
11	35	Catarrhal icterus ⁴	0.95	0.95	0.95	1.04	1.09
12	36	Carcinoma ventriculi involving pancreas (autopsy) ⁵	0.66	0.66	0.66	0.68	1.03

¹ The Roentgen ray in this case showed a markedly elongated stomach, reaching five fingers' breadth below the left crest of ilium; it was atonic and emptied very slowly. The urine showed traces of sugar several times. Glycemia, 102 mg. per 100 cc. of blood.

² Icterus lasting two months, serum bilirubin, 16. Glycemic curve, after glucose and after levulose of the liver type. Duodenal secretion contained bilirubin, 5; ferments: trypsin, 7; diastase, 7; lipase, 8 units. Gastric analysis: Free hydrochloric acid, 40 per cent; total acidity, 75 per cent.

³ Purulent pericholecystitis. Acholic stool. Duodenal secretion had no bilirubin. Ferments, 10 per cent.

⁴ Catarrhal icterus. Icterus lasted over three months. Serum bilirubin, 5 units (one month before when patient was admitted it was 20 units). Stool somewhat colored. Urine contained no bilirubin.

⁵ Roentgen ray findings: Carcinomatous narrowing of prepyloric portion of stomach, carcinomatous infiltration of gastric wall. Gastric analysis: Free and total acidity, 0; ferments, 15 per cent. Occult blood present in stool. Duodenal secretion: Trypsin, 9; diastase, 9; lipase, 4; blood diastase, 3 units. Glycemic curve after glucose showed blood sugar amounting to 50, 150, 250, 338, 274 and 182 mg. per 100 cc.; with glycosuria at the end of first hour, 0.8 per cent.

Whereas the previous cases show merely a derangement in the absorption of fats from the intestines because of lack of bile and of the pancreatic lipases, the cases in the last group (Table III) show derangements of fat metabolism in the tissues. In the 3 cases of diabetes (Cases 13, 14 and 15) the first 2 had a glycemia of about 200 mg. per 100 cc. and no acidosis with a normal lipemia; the third case entered with a severe acidosis, with a glycemia of 600 mg. per 100 cc., lipemia 1.3 per cent and an alkali reserve of 12 per cent. After fourteen days of intensive treatment with insulin the glycemia fell to 400 and the lipemia to 0.64 per cent. In all 3 of these cases the lipemic curve differed from the normal curve, the lipemia rose earlier, reached higher values, and the quotient ratio was 1.4 to 1.58

and even after six hours still had a tendency to rise. In diabetes the lipemic curve appears to be quite analogous to the glycemic curve, and this analogy demonstrates the relation between the fat metabolism and the carbohydrate metabolism. During the course of lipemic curves in cases of obesity (Cases 16 and 18) and in dystrophy adiposogenitalis (Case 17) we can note an analogy to the

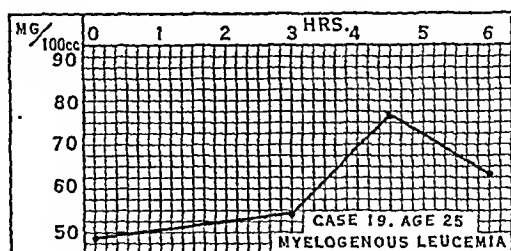


CHART IV.

prediabetic curve in obesity which is also found in Case 16, in which there is a high quotient and a prolongation of the downward curve. On the other hand, in the last case of myelogenous leukemia (Case 19) there is a similar curve. How far the spleen or reticuloendothelial system plays a rôle here, we are not in a position to say.

TABLE III.—ABNORMAL ABSORPTION OF FAT FROM INTESTINE.

Case No.	Age.	Diagnosis.	Fasting lipemia, per cent.	Lipemia (per cent) after ingestion of fat.				Ratio of fasting to maximum lipemia.
				1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	
13	21	Diabetes mellitus (glycemia, 262 mg. per 100 cc.; glycosuria, 1.2 per cent; no acetone)	0.58	...	0.68	0.89	0.92	1.58
14	22	Diabetes mellitus (glycemia, 206 mg. per 100 cc.; no glycosuria, acetone or acetoacetic acid)	0.67	0.70	0.89	0.95	0.95	1.41
15	27	Diabetes mellitus ¹	0.64	...	0.83	0.86	0.90	1.40
16	44	Obesity; hypophyseal tumor ²	0.50	0.51	0.56	0.72	0.63	1.44
17	24	Dystrophy adiposogenitalis (hypopituitary); hypothyreosis ³	0.55	...	0.70	0.83	0.67	1.51
18	40	Mitral insufficiency; angina pectoris; obesity; menopause; wt., 95.4 kg.	0.56	...	0.62	0.74	0.69	1.32
19	25	Myelogenous leukemia ⁴	0.48	...	0.54	0.77	0.63	1.60

¹ Entered in coma; glycemia, 500 mg. per 100 cc.; acetoneuria, 2+; acetoacetic acid, +; alkali reserve, 12; lipemia, 1.3 per cent. Fourteen days after entrance, on the day of experiment, glycemia was 400 mg. per 100 cc. and glycosuria 1 per cent; there was no acetone. This patient received daily over 100 units of insulin.

² From 1917 to 1919 the patient's weight increased from 70 to 125 kg. Since then the weight had been around 120 kg. (264 pounds). The nasal aperture continuously expanded; the skin was getting rougher; headaches occurred. Eyesight and smell were normal. Glycemic curve after 50 gm. glucose showed blood sugar amounting to 130, 190, 210 and 158 mg. per 100 cc. Urine sugar, +, but — two hours later. Basal metabolism, —11 per cent. Specific dynamic action of protein after ingestion of 170 gm. of ham raised the basal metabolic rate 30 per cent. Roentgen ray showed irregular enlargement of the sella turcica.

³ Since childhood the patient had been small and fat; studied well. Menstrual periods started at age of eighteen, none since then. Had frequent headaches. Urination normal. Weight, 59.6 kg. Roentgen ray showed a total ossification of sella turcica. Vision normal. Liquids were excreted in a normal fashion; urine concentration normal. Specific dynamic action of protein after ingestion of 200 gm. of ham raised basal metabolic rate from —16.5 per cent to +5 per cent in sixty minutes.

⁴ The spleen filled nearly the entire abdomen and reached clear to the crest of ilium distally between the umbilicus and symphysis pubis, on the right to the midclavicular line.

This report was not meant to go any further into the theoretical considerations as much more work will be necessary before we can come to any definite conclusions.

Summary. 1. In a normal individual hyperlipemia appears between the second and third hours after the ingestion of fat, and reaches its maximum between the fourth and fifth hours, returning to its original value during the sixth hour.

2. In the series here reported, in cases of gastroparesis with atony, asthenia of the pancreas, mechanical icterus, carcinoma of the stomach involving the pancreas, the lipemia either did not change during the first six hours or else there was a slow rise of the lipemia level during the period in which, normally, lipemia is decreasing.

3. In diabetes the lipemia rose earlier, reached a higher level, and even after six hours still had a tendency to rise. The lipemic curve in diabetes appears to be quite analogous to the glycemie curve. This analogy demonstrates the relation between the fat metabolism and the carbohydrate metabolism.

4. In obesity and in adiposogenitalis and dystrophy, myelogenous leukemia, the leukemic curve is analogous to the prediabetic curve.

REFERENCE.

- 1 Vanysek: *Cas. lek. cesk.*, 1924, vol. 63, 77.

ATROPHY OF SUBCUTANEOUS FAT ASSOCIATED WITH INSULIN INJECTIONS.*

By JOHN B. NICHOLS, M.D.,

MEDICAL DIRECTOR, ACACIA MUTUAL LIFE ASSOCIATION, WASHINGTON, D. C.

DURING the past three or four years there have appeared in medical literature a number of reports of cases of atrophy of the subcutaneous fatty tissue at or near localities in which insulin injections have been made over considerable periods of time. The condition is illustrated by a case which has come under my observation, the particulars of which are as follows:

Case Report. The patient, a widow, had lived an active life, and been subjected to much strain. She had had 2 children—a daughter, dying of diabetes at the age of twenty-two years, and a son, now living at the age of thirty years, also a diabetic. Her weight at the age of twenty-five years was 165 pounds; height, 64 inches. At the age of forty-four years she had a vaginal operation for uterine fibroids, with no subsequent hemorrhage; Roentgen ray at present shows an opaque rounded mass in the pelvis, apparently a calcified fibroid. A benign tumor was removed from her left breast at the age of forty-nine years.

In 1924, at the age of fifty-five years, she was discovered to have diabetes, with urinary sugar, 7.9 per cent; and fasting blood sugar, 340 mg. in 100 cc.; there was also some nephritis, with hypertension (to 220 systolic), and

*Read before the Medical Society of the District of Columbia, March 19, 1930.

cardiac arrhythmia; weight, 102 pounds; chief complaint, asthenia. Dietetic and insulin treatment was instituted in September, 1924, and kept up faithfully for a few months, with satisfactory improvement. The nephritis and hypertension largely subsided. Her weight in April, 1925, had increased to 134 pounds.

During the next four years the insulin injections, 20 to 30 units daily, were continued, but the dietary regimen was faulty.

During the winter of 1926-1927 she discovered that there was a complete disappearance of the subcutaneous fat over her lower abdomen, involving in general a circular or oval area from the navel to the pubes. There were also several similar atrophic depressions or hollows "bigger than hickory nuts" in the anterointernal aspects of both thighs. The insulin injections had been administered in the outer part of the lower third of both thighs, several inches below the atrophic areas; and in the outer iliac regions of the abdominal wall on both sides, external to the location of the suprapubic atrophic area. The disappearance of the fat had been entirely unaccompanied by any pain or other symptoms. The injections were made aseptically, and no infection had occurred. The patient's weight at this time was 100 pounds. She subsequently changed the site of the injections to the arms.

In May, 1929, the patient again came under my observation, complaining especially of insomnia, severe nocturnal pains in the back and trunk, marked constipation and dysuria. There was some ataxia of station and gait and enfeeblement of the reflexes; diabetic myeloneuritis or pseudotabes was diagnosed by a neurologist. Her weight was 125 pounds; there was hyperglycemia and high urinary sugar; Wassermann and Kahn reactions negative; other conditions negative or irrelevant.

In the suprapubic region of the lower abdomen there was a considerable area, as large as the palm of the hand, where the subcutaneous fat was completely atrophied and absent, and the thinned fatless cutis lay directly on the abdominal fascia and muscles, over which it was very freely movable, and the markings of which were plainly palpable and almost visible. This atrophic area extended below to the pubes; above it was bounded by irregular abrupt and thick rounded edges of the subcutaneous fatty tissue extending downward in several projections into the atrophic region. The area of atrophy was stated to have originally extended to the navel; but over the upper half the adipose tissue had regenerated and was growing downward by several projecting masses of full thickness and with abrupt rounded edges or promontories into and gradually filling up the depressed area. The defect was being replaced not by general deposition of new fatty tissue over the entire defective area, but by growth and advance of the panniculus adiposus in its entire thickness from above downward. Although the disappearance of the fat in the first place had been unattended with any pain or sensation, the regeneration of the masses of fat was accompanied by severe and constant local pain and soreness, of which the patient bitterly complained.

In the anterointernal regions of both thighs there were several rounded depressions formed by similar defects of the underlying fat. These had originally been much larger; but regeneration of the adipose tissue had been in progress and lessened their size.

The subsequent course of the case has no bearing on the adipose atrophy. The diabetic conditions were improved; but the psychoneurotic history for a time was stormy.

At the present time (December, 1929), seven months later, the regeneration of the fat has progressed markedly. The depressions in the thighs have almost disappeared. The large suprapubic defect has been filled with new adipose tissue over its entire base; but the surface still shows a number

of deep, rounded depressions, giving an irregular undulating contour to the skin. The pain formerly associated with the regeneration of the fat has entirely ceased.

The earliest report of local fat atrophy following insulin injections appears to have been one of 5 cases by Depisch, in October, 1926; Barborka, of the Mayo Clinic, independently observed and reported 2 cases in November, 1926. In 1927 2 cases were reported by Davison, and Méntzer and duBray; in 1928, 17 cases, by Carmichael and Graham, Chapman, Rabinowitch, Preisel and Wagner and Awrounin (Avery); and in 1929 I have found a report of 8 cases in children by Fischer; a total, including my report, of 35 cases. A special collection and review of the data of 21 of the cases was presented by Avery in 1929.

It is probable that the condition, if borne in mind and looked for, would be found to occur more frequently than the paucity of the cases heretofore reported would indicate; since Depisch alone saw 5 cases, and Rabinowitch found 8 cases in the metabolism clinic of the Montreal General Hospital. Fischer, among 24 children who had been receiving insulin injections for more than six months, found 8 marked cases of the atrophy, and 8 slight cases; while only 2 out of 15 children failed to show some atrophy after more than one year of insulin treatment. Similar statistics for adults have not yet been presented.

The lesions consist of areas of atrophy and disappearance of the subcutaneous fat at or near the sites where hypodermic insulin injections have been administered over a considerable period of time. They therefore usually occur on the thighs or arms; or over the abdomen, as in my case. In the most marked cases, there are large areas, sometimes reaching the size of the palm of the hand, where the panniculus adiposus is completely absent and the thinned fatless cutis lies directly on the underlying muscular and facial structures, which are distinctly and startlingly palpable, and even almost visible. The less extreme or moderate cases consist of oval or oblong depressed areas of the skin, or rounded depressions like large dimples. In the slightest perceptible traces of the condition there is merely a slight flattening of the skin with a little thinning of the panniculus, more evident to palpation than to sight. The cutis is probably ordinarily unchanged, and freely movable over the underlying fascia; although induration of the skin has been noted, and also adhesion to the underlying structures.

The atrophic areas are not necessarily situated at the exact sites of the injections, but may be located at a little distance in their neighborhood, perhaps in the course of the lymphatic drainage away from the injections. There are frequently several of the lesions present in each affected individual.

The development of the atrophy is unattended with pain or other subjective symptoms; there is no indication of any inflammatory

process, nor of any neural participation or etiology in the changes. The condition may not be noticed until after it is fully developed. The process is apparently exclusively an atrophy of the fatty cells or adipose tissue, and no other tissues or cells are involved. In the case of Mentzer and duBray "sections taken from the depressed areas showed no lymphocytic foci indicative of inflammatory changes;" in this case a small calcified nodule a centimeter in diameter was situated contiguous to the depression.

In the reported cases the duration of insulin injections prior to the appearance of the atrophy has ranged from three months to three and a half years. The antecedent duration of the diabetes has varied from six months to eighteen years. The dose of insulin has been from 10 to 120 units daily, injected from one to three times a day. It is noted in several of the cases that although insulin was taken, the dietary regimen was faulty. Body build has no bearing on the development of the lesions, as some of the patients have been obese, others slender. The duration of the period of development of the atrophies, from their first inception to the attainment of full size, is not indicated in the reports.

As to sex, so far as stated, 7 cases occurred in males, 16 in females; apparently indicating somewhat greater susceptibility of females.

All ages are susceptible. Fifteen of the reported cases occurred in children, in the first and second decades; the details of the ages and sex are not stated. Possibly children, with their more delicate tissues, are more subject to the atrophy than are adults; this perhaps also explains the greater susceptibility of females. Of 20 cases in adults, 2 occurred at the ages of twenty to twenty-nine years; 6 from thirty to thirty-nine; 4 from forty to forty-nine; 7 from fifty to fifty-nine; 1 at sixty.

In only 2 of the cases is regeneration of the atrophied tissues noted, the other case reports not having covered sufficiently long periods of observation. In Chapman's case, insulin had not been used for two and a half years, and the affected thigh had returned to normal. In my case, over a period of three years there has been extensive regeneration, although not yet complete; in this case the regeneration was attended with severe local pain and soreness (perhaps comparable with that of adiposis dolorosa). From these two cases it appears probable that after cessation of the injections complete regeneration from extensive atrophy may be expected in the course of two to four years.

Various explanations of the causation of the atrophic process have been considered, but no final conclusion has been reached.

That it is a result of the diabetic condition *per se* is unlikely. Diabetes, it is true, involves a disturbance of fat metabolism, but that is of a biochemic nature general in its operation, and not a local histolysis. No cases have been reported in diabetes except in conjunction with the use of insulin.

Antiseptics used for sterilization can be eliminated as causative, since various methods of disinfection were used in the cases—alcohol, cresol, lysol, boiling. Infections have not been responsible. Faulty technique of the injections has been blamed, especially their limitation to a too restricted area; but this can be only a secondary factor. Contamination or peculiarities of the make of insulin employed can be excluded, since the insulin used in the reported cases came from several different sources.

It is natural to suspect the local action of the insulin itself as the specific cause of the fatty atrophy. Insulin is a pancreatic product. One of the active properties of the pancreatic secretion is lipolysis. Fatty necrosis is one of the results of pancreatic disease. Lipase is not, however, supposed to be present in the commercial preparations of insulin; and Rabinowitch was unable to detect its presence in concentrated preparations. This does not exclude the possibility that a precursor of the enzyme is present, which in contact with the body fluids becomes activated and exerts lipolytic properties.

It is well known that the oxidation of fat in the body is largely effected by the oxidation of the carbohydrate; as it is frequently expressed, fat burns in the flame of carbohydrate. My own suggestion as to the causation of the fatty atrophy in these cases is this: that the strong initial concentration of insulin in the subcutaneous tissues near the site of injection causes an active local oxidation of carbohydrate, which in turn causes an active combustion of the local fat.

Another causative possibility is open for consideration. Is the atrophy due to long-continued frequently repeated traumata or other effects involved in the hypodermic injections as such, independently of the insulin? Data for adequate comparison are lacking, since in no other common conditions is hypodermic medication so prolonged and intensive as in diabetes. However, Mentzer and duBray state that in narcotic addicts they have observed several instances of atrophy of subcutaneous fat; microscopic examination of these lesions invariably showed foci of lymphocytes and polymorphonuclear leukocytes, indicating an inflammatory condition different from the apparently purely atrophic process of the insulin lesions.

Avery considers the lipodystrophy from insulin as a "traumatic atrophic panniculitis," due to the repeated hypodermic traumata. He bases his theory on 2 cases of definitely inflammatory panniculitis, with atrophy, which he cites; these cases were, however, entirely different in character from insulin atrophies, and would not seem to have any bearing on the pathology of the latter.

Lawrence reported results of microscopic examinations of skin from areas where many insulin injections had been made (not from patients with fatty atrophy); he found only a tendency to slight fibrosis and increase of connective-tissue cells in the subcutaneous fat.

Bowie and Robinson on examination of sections from the infiltrated areas of the skin of rabbits soon after insulin injections were made found only, aside from the wide separation of the cells, degenerative changes in some of the superficial muscle fibers; but similar changes occurred after injection of other solutions not containing insulin.

In the way of treatment, it is obvious that injections in the vicinity of the affected areas should be discontinued. As a preventive measure, the sites of the injections should not be confined to limited areas, but should be occasionally changed and well distributed.

Summary. Prolonged hypodermic administration of insulin sometimes causes atrophy of the subcutaneous fatty tissues in the vicinity of the injections. In this paper a case of the kind is reported and 34 other cases in the literature are reviewed.

BIBLIOGRAPHY.

1. Avery, H.: *British Med. J.*, 1929, i, 597.
2. Awrounin (Avery), H.: *Proc. Roy. Soc. Med., Clin. Sec.*, 1928, 22, 156.
3. Barborka, C. J.: *J. Am. Med. Assn.*, 1926, 87, 1646.
4. Bowie, D. J., and Robinson, W. L.: *J. Lab. and Clin. Med.*, 1923, 8, 569.
5. Carmichael, E. A., and Graham, G.: *Lancet*, 1928, i, 601.
6. Chapman, P. D. H.: *Ibid.*, p. 674.
7. Davison, R. A.: *California and Western Med.*, 1927, 26, 210.
8. Depisch, F.: *Klin. Wchnschr.*, Berlin, 1926, 5, Part II, 1965.
9. Fischer, A. E.: *Am. J. Dis. Child.*, 1929, 38, 715.
10. Lawrence, R. D.: *Lancet*, 1928, i, 1328.
11. Mentzer, S. H., and duBray, E. S.: *California and Western Med.*, 1927, 26, 212.
12. Preisel, R., and Wagner, R.: *Ztschr. f. Kinderh.*, Berlin, 1928, 46, 453.
13. Rabinowitch, I. M.: *Canadian Med. Assn. J.*, 1928, 18, 560.

A CLINICAL STUDY OF ONE HUNDRED AND THREE CASES OF SCLERODERMA.*

By PAUL A. O'LEARY, M.D.,

HEAD OF SECTION ON DERMATOLOGY AND SYPHILOLOGY, THE MAYO CLINIC AND
PROFESSOR OF DERMATOLOGY ON THE MAYO FOUNDATION FOR MEDICAL-
EDUCATION AND RESEARCH, GRADUATE SCHOOL, UNIVERSITY OF
MINNESOTA, ROCHESTER, MINN.,

AND

RUBEN NOMLAND, M.D.,
CHICAGO, ILL.

SCLERODERMA is chronic dermatosis characterized by diffuse or localized induration, pigmentation and sclerosis of the skin. The manifestation varies from small single patches to involvement of the entire tegument; hence it is divided into two types, the diffuse or generalized, and the localized.

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The diffuse form of scleroderma (Fig. 1) may begin with symptoms of arthralgia, malaise, loss of weight and asthenia, or with vasomotor phenomena in the extremities similar to the type found in Raynaud's disease. The course of the disease varies as to the extent and degree of involvement; it may remain stationary for years, and rarely it may disappear without sequelæ. Numerous cases have been observed in which the induration disappeared, leaving profound atrophy of the skin, but more frequently there is slow but continuous progression of the disease until death results.

Circumscribed scleroderma includes the three varieties of the disease known as morphea (Fig. 2), scleroderma in bands (Fig. 3), and guttate scleroderma. The circumscribed type most commonly begins as a single, rarely several, and more rarely as many white, pink, or slightly congested patches. These patches spread peripherally, showing a lilac-colored border, while in the center of the plaque, pigmented or whitened atrophic patches develop. Occasionally in the early phase of the circumscribed form, the elevated, ivory-yellow indurated characteristic patches of the diffuse form of scleroderma may be seen.

In the data considered here, 103 cases were studied. There were 48 cases of generalized scleroderma and 55 cases of the various forms of circumscribed scleroderma.

Generalized or Diffuse Scleroderma. It is essential to know the features that characterize the onset of the generalized type of scleroderma, because during this phase of the process other diseases may be simulated. There are two common types of symptoms in the beginning. Pain, swelling and stiffness of the joints, usually of the hands, but often diffuse and accompanied by systemic symptoms, were found in 58 per cent of the cases of generalized scleroderma. Vasomotor symptoms in the extremities, of varying severity, were found in 33 per cent. In only 8 per cent was none of these symptoms present at the beginning. These data are at variance with the general conception of the disease, which is that the onset is unaccompanied with premonitory symptoms.

Symptoms. Osler,²⁸ in 1898, reported in detail 8 cases of scleroderma. In 5 of these there were symptoms of an arthritic nature which varied from generalized recurrent arthritis to swelling and stiffness of the hands. In one case there was vasomotor disturbance of the hands and feet strongly suggestive of Raynaud's disease. The occurrence of acrocyanosis, aeroasphyxia and other symptoms suggestive of Raynaud's disease has been noted by many writers. Vasomotor disturbances of the extremities was less common than arthritic symptoms in our series, but such disturbances seem to have attracted more attention in the literature. Among writers who specifically have emphasized these vasomotor phenomena are Hutchinson, Castle, Favier, Thibierge and Weissenbach, Scholefield and Weber, Alquier and Touchard, and Longeoepe.

In the group of 48 cases of generalized scleroderma, 28 (58 per cent) presented arthritic symptoms as the earliest manifestation of the disease. The extent and severity of the symptoms in the joints were extremely variable. The milder cases evidenced only a little pain, swelling and stiffness in the hands, followed by hardening of the skin, whereas in the extreme cases there was generalized severe pain of joints and muscles, with swelling and stiffness, often accompanied by general prostration and extreme loss of weight. Except for the scleroderma, the symptoms simulated severe generalized arthritis. The differential diagnosis was often difficult, but usually was evident when hardening of the skin was noted and appreciated.

Of the 28 cases in which symptoms of arthritis were present, the original symptoms were in the hands in 12. In many of these the pain in the joints later became more general. In 7 cases there was involvement of all extremities in the beginning. In 3 cases, the condition began in other joints. In 6 cases, there was generalized pain and stiffness in the joints, loss of weight and systemic symptoms. Because of the outstanding arthritic symptoms, roentgenograms of the hands were taken in 16 cases of scleroderma and sclerodactylia. In 6 of these, the roentgenographic evidence was negative. In 4 cases, there was marked periarticular arthritis. In 1 case it was slight. In 2 cases there were destructive changes of the bones of the hands. In 3 cases, there was loss of the distal phalanges of ten, three, and two fingers, respectively; this condition is not infrequent in the late phases in the cases in which the disease is extensive.

In 4 of the cases of the generalized type, the onset of the disease was first noted by the thickening of the skin of the upper part of the trunk and the face, unaccompanied by constitutional symptoms. In 1 of these cases, of the edematous type, edema of the eyelids and face was the first symptom noted.

The occurrence of vasomotor phenomena in the extremities was the next most common initial symptom. This occurred in 16 of the 48 patients with generalized scleroderma (33 per cent). The hands were always involved and in a great many cases the feet were also involved. The severity of the symptoms was exceedingly variable. In the milder cases, only moderate cyanosis was present on exposure to cold. In the more severe cases, there was evidence of all the typical symptoms of Raynaud's disease: the white, blue and red stage and the accompanying pain. In the severe cases, of which there were 3, there was spontaneous gangrene with loss of the distal phalanges following this syndrome. Trophic ulcers of the extremities, especially of the fingers, were fairly common in this group, more so than in the group in which the onset was characterized by arthritic symptoms. Cases of this type of scleroderma with sclerodactylia were not included unless there was scleroderma elsewhere. The associated scleroderma was most commonly found in the thorax and in the face, which was without wrinkles, masklike and stiff.

SCLERODACTYLIA. Brown and O'Leary⁸ studied the capillaries of the nailfold in 5 cases of scleroderma with sclerodactylia (Fig. 4). They compared these capillaries with the capillaries in true Raynaud's syndrome with secondary changes in the skin. The most common and almost characteristic change in these cases of sclerodactylia was the presence of giant feathery capillary loops with only a uniform flow of blood. There was little response or change in the flow when the extremity was exposed to cold or friction. Gitlow and Steiner¹⁴ found similar giant capillaries in a case of sclerodactylia which they studied carefully. Brown⁷ described the appearance of the capillaries in Raynaud's disease, and called attention to the fact that the morphologic changes in the capillaries are slight but the disturbances in the flow of blood and the response to changes in temperature are more marked. In contrast, the capillaries of the nailfold, in the cases of generalized scleroderma without sclerodactylia, appeared normal.

Sclerodactylia was noted in all except 5 cases of generalized scleroderma. In other words, generalized scleroderma is almost always accompanied (89 per cent) by sclerodactylia. These observations compare favorably with those in the 68 cases of generalized scleroderma reviewed from the literature by Robinson. He found involvement of the fingers in 60 of the 68 cases; in 35 cases the disease appeared first in the hands or fingers.

Sclerodactylia may be said to be of three types: (1) True scleroderma of the fingers with mild vascular changes; (2) the vascular type in which sclerosis of the skin develops after the symptoms of disease of the bloodvessels are noted; (3) a mixed type in which it is impossible to determine whether the dermal or the vascular changes took place first. Moderate experience with scleroderma will permit of the clinical impression as to whether the vascular or the sclerodermic process predominates. A study of the capillaries of the nailfold as a rule substantiates this conception.

Systemic symptoms of a general nature, as has been mentioned, are often outstanding. Evidence of the severity of generalized scleroderma is well shown by the loss of weight, which is often extreme. One patient in this series lost 76 pounds (34.5 kg.). The loss of weight is as a rule closely paralleled by the degree of asthenia, the extent of the disease, the extent of scleroderma, and the constitutional symptoms. Clinical facts of general application were not brought out by the general examinations of these patients. Special studies of the basal metabolic rate and of intoxication by arsenic were made in many cases; the results will be reviewed presently.

CALCIFICATION OF THE SKIN. Calcification of the skin may also be found in extensive cases of generalized scleroderma. Osler and McCrae²⁹ called attention to it, emphasizing that deposits of cal-

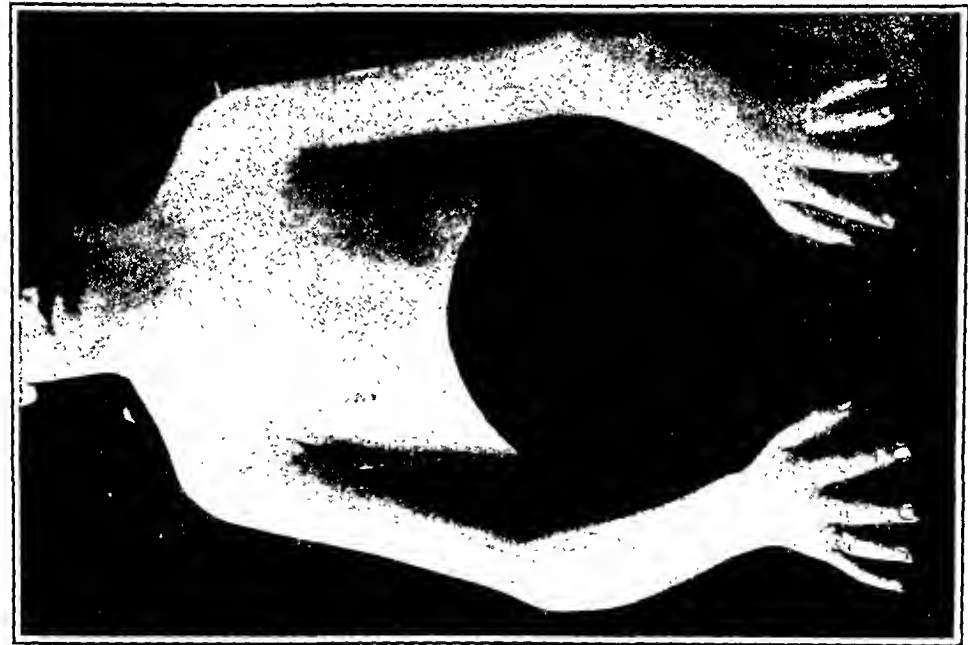


FIG. 1.—Generalized scleroderma.



FIG. 2.—Morphea.



FIG. 3.—Linear scleroderma; developed following a blow to shoulder.

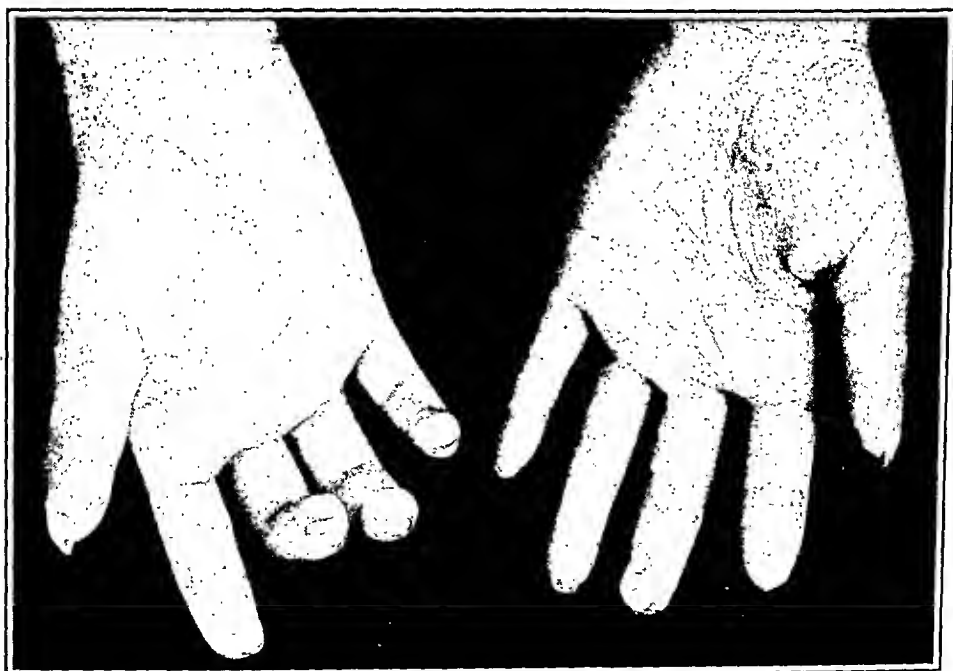


FIG. 4.—Sclerodactylia, showing ulceration of finger tips and changes in the nails.

cium occur usually on the fingers and simulate the tophi of uric acid which occur in gout. Thibierge and Weissenbach presented³⁶ a case of generalized scleroderma with deposits of calcium. They reviewed adequately 8 other cases reported by various authors, and emphasized that the diagnosis can only be made certain in one of two ways: the demonstration by the roentgenogram of the presence of calcium salts in the nodules, or the ulceration of calcareous nodules and the extrusion of chalky material which may be recognized by chemical examination. In our series, 2 cases of generalized scleroderma with localized calcification were observed. One case was proved by chemical analysis of the extruded chalky material to contain calcium phosphate and calcium carbonate. Biopsy in the second case did not reveal calcium salts which ordinarily may be found deep in the derma, but chalklike material was later discharged from the wound.

Calcification of the skin has often been noted in association with other types of dermatosis. Weidman and Schaffer reported a case in which there were deposits of calcium in almost all elements of the skin, including the cells of the epidermis, arteries, nerves, sweat ducts and sweat glands.

A patient who had all the clinical symptoms of extensive, severe generalized scleroderma was seen at The Mayo Clinic in 1921. The roentgenogram revealed extensive diffuse calcification of the subcutaneous connective tissues, most marked in the extremities. At postmortem examination the presence of extensive generalized inflammatory and sclerotic changes in the muscles as well as in the skin with deposits of calcium phosphate and calcium carbonate, changed the diagnosis to myositis ossificans.

Circumscribed Scleroderma. Circumscribed scleroderma (Fig. 2), also called morphea, on the contrary, is not accompanied by general symptoms or vasomotor phenomena. Usually there are no associated subjective symptoms, and unless the plaques are numerous or their situation is the cause of disfigurement, the lesions go undiagnosed. Scleroderma in bands (Fig. 3), a form of circumscribed scleroderma, if extensive may cause deformity and some atrophy of one or more extremities. A history of trauma frequently precedes the onset of this form of the disease. Ormsby said: "Patches of morphea commonly begin as red or violaceous areas, fingernail to palm size or larger, and increase in size rapidly or slowly. In a variable period of time the center of each patch becomes whitish or yellowish while the peripheral portions of the plaque are purple or violaceous." In 55 cases of circumscribed scleroderma reviewed in this study there was morphea in 38, morphea guttata in 3, and scleroderma in bands in 14. In more than half of the cases the condition began as a single, whitish-pink or scarlike spot; rarely there were several spots. In a few cases the onset was ushered in with localized thickening of

the skin and in 3 cases, with multiple small white spots. Residual brownish pigmentation and the atrophic center of the patch was the rule in these cases.

Osborne, in 1922, reported from The Mayo Clinic 3 cases of morphea associated with facial hemiatrophy. Since then we have observed 3 other cases of morphea and facial hemiatrophy in one of which there was atrophy of the entire right side of the body. The frequent association of morphea and hemiatrophy would tend to corroborate the conception that injury to the nerve from trauma or other causes was a factor in the production of the entity. Hutchinson believed facial hemiatrophy to be a manifestation or residuum of facial morphea. Gans also classified facial hemiatrophy as a manifestation of scleroderma.

Pathology. A study of the histopathology of scleroderma has thrown little light on the cause of the disease. The histopathologic changes, however, indicate that the process is the result of a systemic disease rather than a localized disorder of the skin. The picture is accordingly a secondary manifestation of this disease. The variety of changes of the skin seen in the various types of scleroderma suggests that different noxae are instrumental in the production of the histopathologic changes. Gans stated that there are three stages in the development of the process: (1) The erythematous or edematous; (2) the indurated; (3) the atrophic. In the indurated stage the most significant changes are noted. In a well-developed case of the diffuse form of the disease Kyrle noted the outstanding changes to be the proliferation of the connective tissue and degenerative changes in the form of homogeneous masses or of individual bundles becoming homogenized. The elastic fibers are not destroyed but may show rarefaction and splintering, and are found between the swollen bundles of collagen. Kyrle stated the belief that the chief pathologic process occurs in the collagen in the nature of colloidal chemical changes.

The histopathologic features of morphea or localized scleroderma are somewhat different from those of generalized scleroderma. The lilac-colored ring noted in morphea is due to the engorgement of the veins of the papillary layer with deposits of pigment about the veins as the result of the stasis. The process extends to and involves the subcutaneous tissue, and the cellular infiltrate is diffuse rather than perivascular. In our study of the cases of both the generalized and localized forms of the disease, the part played by the bloodvessels in the production of the disease seemed an important one. Early in the process many of the bloodvessels are dilated and surrounded with fixed connective-tissue cells, lymphocytes, and a few plasma cells. The intima of the bloodvessels proliferates, becomes swollen, and may almost obliterate the lumen, although the media remains unchanged. The changes in the connective tissue follow as a result of the cellular infiltrate. Later on, it is noted that the bloodvessels

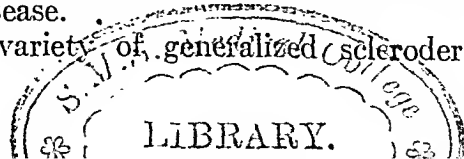
are narrowed and atrophied, and, as the process extends, all of the adnexa of the skin likewise become atrophied.

The pigmentation in the generalized form of the disease is seen at the borders of the sclerodermatous areas and is due to the deposits of melanin in the basal-cell layer of the epidermis and occasionally in the chromatophores of the cutis.

Diagnosis. An established case of generalized scleroderma may be readily diagnosed by one who has had little experience with the disease; however, the recognition of the disease during its early manifestations often presents a difficult diagnostic problem. The onset with symptoms of arthritis or with vasomotor disturbances in the extremities must be borne in mind. In an early case, the patient often complains of stiffness of the skin before the sclerosing process is visible or palpable. At this time the limitation of motion, the decrease in the normal wrinkles of the skin, a sheen of a slightly waxy hue and the loss of expression, if the face is involved, are among the early manifestations. It is also at this time that the sclerodactylia may become manifest although it may require observation for several months before a definite diagnosis is possible. In the advanced case with sclerodactylia the hands are stiff and cold. The skin of the hands is hard, suggesting the wax hand of a moulage, ivory-yellow and unwrinkled. On palpation and pinching, the fixedness suggests the skin of a pig. If the face is involved it presents a stiff masklike appearance, as in Parkinson's disease. The normal furrows in the skin are ironed out and the patient often cannot wrinkle the forehead. Expressions of emotion are absent, the opening of the mouth is limited, due to sclerosis of the skin of the cheeks, and the speech may be indistinct. The skin of the torso and legs presents varying degrees of induration and sheen, depending on the extent of involvement.

The early manifestations of generalized scleroderma are often erroneously diagnosed chronic arthritis, not only because of the pain and stiffness of the joints, but because roentgenologic changes suggestive of those in chronic arthritis are often found in the hands of patients who have sclerodactylia. Therefore, mild roentgenographic changes must be disregarded in the diagnosis. In the cases in which vasomotor disturbances are prominent, the distinction from Raynaud's disease is often difficult, and unless the masklike facies or other evidence of scleroderma elsewhere is present, the diagnosis cannot be made without subsequent observation. For the present, patients who present outstanding vasomotor phenomena of the hands with slight induration in the skin of the hands and no evidence of scleroderma elsewhere, must be considered as having Raynaud's disease. It is in this group that studies of the capillaries of the nailfold will often permit of a differential diagnosis early in the course of the disease.

The edematous variety of generalized scleroderma, which is



uncommon, may be confused with other conditions causing edema of the face. The brawniness of the edema and the presence of scleroderma and atrophic changes in the skin elsewhere on the body will ordinarily make the diagnosis clear. In the few cases in which the fingers are not involved in diffuse scleroderma, the diagnosis is made on the physical changes in the skin, particularly of the face and the upper part of the thorax and neck.

In the cases of generalized scleroderma which have produced atrophy of the skin, distinction must be made from aerodermatitis chronica atrophicans and other forms of idiopathic cutaneous atrophy. The tight "straw" atrophy of scleroderma is readily distinguished from the loose, tissue-paperlike atrophy of idiopathic atrophy. We considered the relationship of the two diseases and expressed a conception with which we are in accord.

As has been mentioned in commenting on calcification of the skin in scleroderma, generalized dermatomyositis may resemble generalized scleroderma closely. Deep biopsy will show the inflammatory and sclerotic changes in the muscles.

Extensive pigmentation of the skin which often accompanies scleroderma may suggest the Addisonian syndrome. The absence of the features of Addison's disease, namely, marked asthenia, low blood pressure, and pigmentation of the mucous membranes, and the lack of scleroderma will distinguish Addison's disease from scleroderma.

Scleroderma in infants is rare. Lieberthal has pointed out the relative benignity of scleroderma in infants compared to scleroderma neonatorum. In this disease the irregularly distributed, well-defined plaques of induration which occasionally have cystlike centers, besides diarrhea, dehydration, and constitutional symptoms often lead to death in a few weeks. Infants with scleroderma, however, usually recover without sequelæ.

The diagnosis of the circumscribed varieties of scleroderma offers fewer difficulties. Morphea usually presents the typical, atrophic ivory or silvery, often pigmented patch with a violaceous halo. It may be quite extensive, involving much of the torso. It is usually confused with still rarer dermatosis, especially with the group of idiopathic types of atrophy, and with atrophic lichen planus. Scleroderma in bands is similar to morphea. It often causes deformities and marked atrophy of the extremity involved, and therefore comes to the attention of the orthopedic surgeon. The guttate type of circumscribed scleroderma is rare and is to be distinguished from other benign types of atrophic dermatosis.

Sex Incidence. A preponderance of females was noted in most of the reports in the literature. Most writers group generalized and circumscribed scleroderma together, which may account for some of the disparity in the series reported. The incidence varies greatly. Thus, Castle reported cases of 11 females and 1 male,

Sequeira reported cases of 18 females and 4 males, Cockayne reported from the literature 104 cases in females and 28 in males, Hutchinson noted 16 females and 11 males in his series, and in Osler's²⁸ 8 cases of generalized scleroderma, 3 were females and 5 were males.

Fig. 5 shows the sex distribution of generalized and circumscribed scleroderma in our group. In both varieties females predominate; 58 per cent of the cases of generalized scleroderma were in females, and 72 per cent of the cases of circumscribed scleroderma were in females. No explanation of this fact has been made, but the great disparity in sex incidence can scarcely be ascribed to coincidence. Circumscribed scleroderma, particularly, has a predilection for the female.

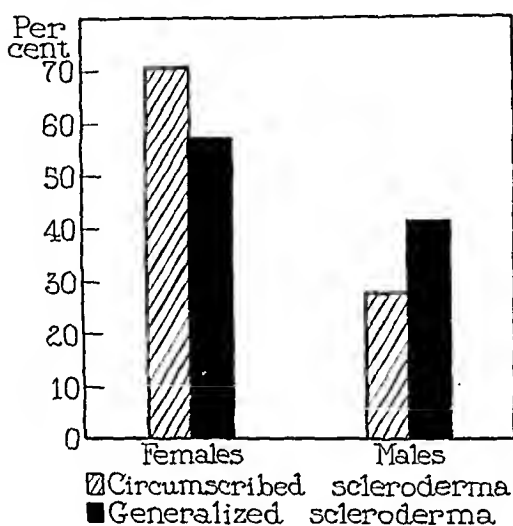


FIG. 5.—Sex incidence.

Age Incidence. Apparently no age is exempt, but adults are more often affected. Lieberthal reported a case of scleroderma in an infant, aged nine days. Goodman reported a case of generalized scleroderma in a girl, aged nine years. He reviewed 16 cases from the literature taken mostly from Levin and Heller's monograph on scleroderma. Cockayne noted the report of 102 cases of scleroderma in children aged less than fourteen years. In Osler's²⁸ cases of generalized scleroderma, the ages ranged from twenty-one to forty years, and in Hutchinson's cases, which were mostly of circumscribed scleroderma, the ages ranged from ten to seventy-five years.

In our series, the ages ranged from eighteen to sixty-six years in generalized scleroderma and from three and a half to sixty-seven in circumscribed scleroderma. Fig. 6 shows clearly the relative and absolute preponderance of circumscribed scleroderma in the first three decades, and the reverse holds true for the fourth, fifth and sixth decades. Both, however, have their maximal incidence in

adult life. A peculiar observation was the great number of cases of scleroderma in bands occurring in the early decades of life. Thirteen of 14 cases occurred in the first three decades.

Etiology. The cause of generalized scleroderma is unknown and no notable advance has been made since the time of Hutchinson, in spite of much study and investigative work, as evidenced by the voluminous literature on the subject. Boardman recently reported a comprehensive review of the literature on the etiology of the disease from which conclusive deductions are not possible. Dysfunction of the thyroid gland has received most attention, but none of the endocrine glands has been slighted. Nervous shock, exposure, infections, syphilis, and pregnancy have likewise been thought to have a causative relation. Chronic intoxication by arsenic has also been proposed as an etiologic factor. Because of the vasomotor symptoms in the extremities in many cases, with the simula-

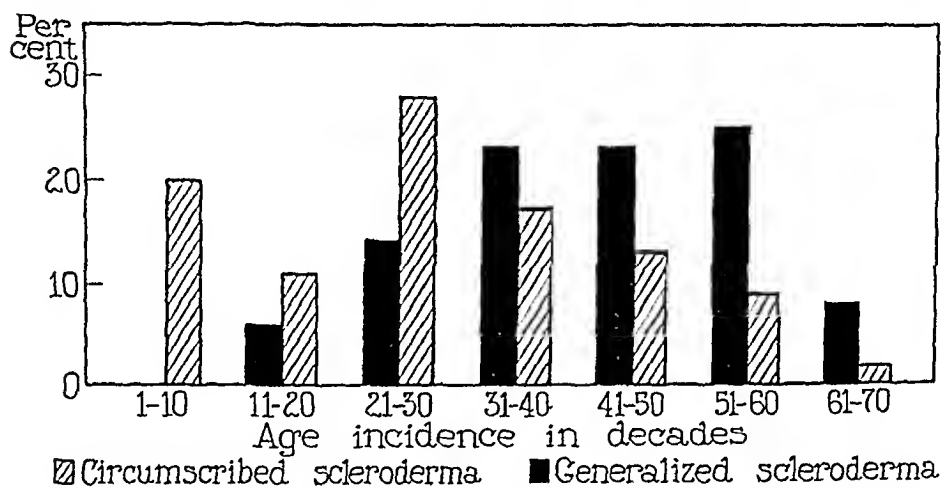


FIG. 6.—Age incidence in decades.

tion of Raynaud's disease, vascular neurosis has entered into the consideration. The hypothesis that it is a disease of unknown varied etiology in which noxae affect chiefly the bloodvessels and collagen of the connective tissue of the dermis, has been proposed by many authors. This hypothesis is based almost entirely on the histopathologic changes in the disease, and is therefore tenable and, to say the least, incapable of disproof at the present time. In a search for possible etiologic factors, special laboratory studies were undertaken to determine the part played by the thyroid gland, changes in blood sugar, the pituitary gland, and arsenic in the urine, in the production of the disease. Likewise particular effort was directed toward the eliciting of a history, either recent or remote, of one of the infectious diseases. The accumulated data are presented in detail.

Castle recently reviewed the literature on the endocrine causation of scleroderma, laying special emphasis on dysfunction of the

thyroid gland. He concluded that the cause is unknown, but that the endocrine glands and the nervous system are etiologic factors. Osler²⁸ was unfavorably impressed with the results of treatment with thyroid extract. Roques, on clinical examination of 31 cases of generalized scleroderma, found that the thyroid gland was small or imperceptible in 14 cases, hypertrophied in 8, and normal in 9. In his review of 67 cases, including his own, he found that 63 per cent of the patients were benefited by treatment with thyroid extracts. Hyde and McEwen and Foerster also commented on the relationship of scleroderma and dysfunction of the thyroid gland. Alquier and Touchard found perivascular sclerosis in the thyroid gland as well as in most other tissues in 1 of 2 cases of generalized scleroderma which came to necropsy. Hektoen and Wells found

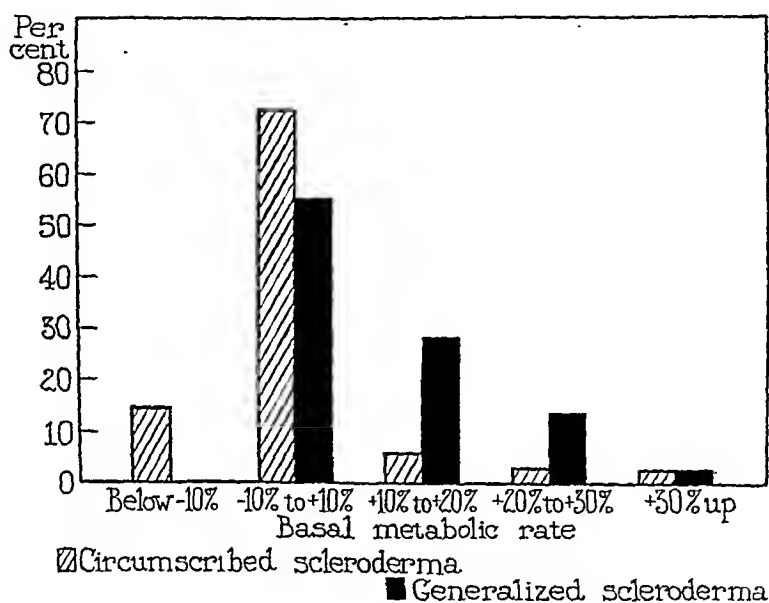


FIG. 7.—Basal metabolic rate.

marked deficiency in the amount of iodine in the thyroid gland at necropsy in a case of generalized scleroderma. Sequeira observed the development of scleroderma in a case of myxedema in which the latter condition was controlled by treatment of the thyroid gland. In Longcope's recent series of 7 cases, the basal metabolic rate was below normal in 3; the lowest rate was -23 per cent.

In our series of cases of generalized scleroderma, dysfunction of the thyroid gland was especially searched for. Determinations of the basal metabolic rate were made in 38 cases of generalized scleroderma. All of these determinations were rechecked to avoid error. In many cases repeated checks were made to determine the effect of administration of thyroxine and dried thyroid gland on the metabolic rate. For purposes of tabulation, the lowest determination of the basal rate was taken (Fig. 7).

In none of the cases of generalized scleroderma was the basal rate below normal. Neither were there any cases in which there was clinical evidence of hypothyroidism. In 17 cases (45 per cent), the basal rate was more than +10 per cent. In 7 of these cases (18.4 per cent of the total) there was evidence of hyperthyroidism, in 2 of which adenomatous goiter with hyperthyroidism was present, and in 1 case, typical severe exophthalmic goiter. In 3 cases the diagnosis of exophthalmic goiter was suggestive but not conclusive. In the seventh case adenomatous goiter with elevation of the basal metabolic rate and suggestive clinical signs of hyperthyroidism were present.

Similar but less extensive studies of the basal metabolic rate were made in 33 of the 55 cases of circumscribed scleroderma (Fig. 7). It will be seen that rates slightly below normal were present in 5 cases (15 per cent of the total) of circumscribed scleroderma. In 4 cases (12 per cent) the rate was above normal. In 2 of these cases hyperthyroidism was present, in 1 case in a severe form with a basal metabolic rate of +64 per cent, and in the other an adenomatous goiter with hyperthyroidism.

Fig. 7 shows that in most of the cases of generalized and circumscribed scleroderma the basal metabolic rates were within normal limits. The few cases in which the rates were below normal approximate the average incidence in a similar unselected group. There is, however, a higher incidence than normal of dysfunction, in that in 7 cases of generalized scleroderma there was either hyperthyroidism or adenomatous goiter with hyperthyroidism besides the scleroderma. A cause and effect relation could not be brought out in the taking of the history, or in the study of the cases clinically. In only 2 cases of circumscribed scleroderma was hyperthyroidism noted.

Other endocrine glands have been thought to be at fault. Castle, in his review, reported a case thought to be due to suprarenal insufficiency in which a graft of the suprarenal gland was attempted without success. Longcope reported a case in great detail in which there was bronzing, asthenia, low blood pressure and low blood sugar. He remarked on the similarity to Addison's disease. In our series, definite or presumptive evidence of Addison's disease could not be elicited. Pigmentation was frequently extreme and asthenia and loss of weight were marked in some cases, but never enough so that a diagnosis of insufficiency of the suprarenal gland could be considered seriously. The blood pressure was almost always normal; in a very few cases it fell as low as 105 mm. of mercury. Pigmentation of the mucous membranes was not noted in any instance.

Longcope also reported the presence of marked hypoglycemia with attacks simulating those following overdosage of insulin in one of his cases. The blood sugar in the others he reported was near the lower limits of normal. In a case reported by Gitlow and Steiner, the blood-sugar curve was normal. Knowles and Ludy reported a

case of diabetes occurring in a patient with generalized morphea. In their case the condition of the skin improved when the diabetes was controlled. In 2 cases of our series, circumscribed scleroderma was associated with mild diabetes and fasting blood sugar of 513 and 221 mg. for each 100 cc., respectively. Studies of the blood sugar were made in 2 cases of generalized scleroderma. The amounts of glucose found were 110 and 98 mg. for each 100 cc., respectively, which is well within normal limits. These data are of course fragmentary, but hyperglycemia with mild diabetes was found in 2 cases, whereas hypoglycemia was not found in the 2 other cases studied.

Disease of the pituitary gland has been suggested by some writers as a possible cause of scleroderma, but the evidence presented is purely hypothetical. In our series, there was no clinical evidence of pituitary changes in any of the cases. Roentgenograms of the pituitary fossa were made in 4 cases, and were found to be negative.

Within the last few years, chronic intoxication by arsenic has also been suggested as a cause of scleroderma. Ayres found arsenic in the urine of 3 patients with generalized scleroderma. Myers and his coworkers emphasized the frequency of arsenic in the urine in scleroderma, but they also found arsenic in many other cases of dermatosis and thus seriously weakened the argument that it was a causative agent. Brooke and Roberts reported on arsenical eruptions seen in Manchester, England, caused by arsenic in cheap beer; they did not observe cases of scleroderma. They saw almost every variety of skin eruption caused by arsenic. In our series, the possibility of intoxication by arsenic was investigated in 23 cases. The tests were usually done on the twenty-four-hour specimen of urine.

The finding of arsenic in the urine of patients with generalized scleroderma was exceptionally difficult to evaluate because medication with arsenic is so frequently given for this disease and also because arsenic was not uncommonly found in the control case. This fact was best brought out by the cases in which large amounts of arsenic were found, and in which arsenic had been given almost uniformly. There were 2 of the 48 cases of generalized scleroderma in which it seemed that chronic poisoning by arsenic was a precipitating or a possibly causative agent of the disease. In the first case, that of a woman in charge of a paint and wallpaper store, there was simultaneous onset of sclerodactylia with scleroderma and arsenical peripheral neuritis. The peripheral neuritis disappeared eventually, but the scleroderma remained. In the second case, that of a worker in a paint factory, scleroderma, mild exophthalmic goiter and symptoms of heavy metal poisoning developed simultaneously. The man was not anemic and lead was not present in the urine. However, arsenic in pathologic amounts was found in the urine. The basal metabolic rate was, moreover, +20 per cent. Osterberg

expressed the belief that traces up to 2 mg. of arsenic in a twenty-four-hour specimen of urine are frequently found in normal persons. This is especially true of heavy smokers. More than 3 mg. of arsenic indicates ingestion, the source of which may not be determined although it is usually found to be due to medication, ingestion of food, cheap chocolate in particular, or occupational exposure to arsenic.

As a control series, determinations of arsenic were made in 19 cases of various other cases of dermatosis. In all of these, less than 3 mg. of arsenic was found in the twenty-four-hour output of urine except in 1 case, in which there was a definite history of the ingestion of arsenic.

Determinations of arsenic were made on the urine in 6 cases of circumscribed scleroderma, in 4 of which arsenic was present in appreciable amounts, from 2.8 to 8.4 mg. in each twenty-four-hour specimen, while in 2 cases the urine was negative for arsenic. An etiologic relationship between generalized or circumscribed scleroderma and chronic poisoning by arsenic could not be established in this study.

Certain authors ascribe systemic infections as the causative factor, either as acute infection simultaneous with or just preceding the onset, or chronic infection such as syphilis.

In our series, acute general infections immediately preceded or occurred with the onset in 6 (12.5 per cent) of the cases of generalized scleroderma. It has been suggested that the dermal symptoms in generalized scleroderma are an expression of a severe, general systemic disease. The preceding infection in these 6 cases was diagnosed influenza three times, tonsillitis twice and erysipelas once. In circumscribed scleroderma general infection occurred only in 2 cases, which were diagnosed poliomyelitis and scarlet fever, respectively.

Of the chronic infections, syphilis, probably because of its ubiquity, has been stressed as a causative factor. Murray-Will, and Audry and Chatellier have emphasized the significance of syphilis as a cause of generalized scleroderma. In our series, clinical investigation for syphilis was carried out, and Wassermann tests were done on 82 of the patients with generalized or circumscribed scleroderma. Two patients with generalized scleroderma had syphilis, and 2 patients with circumscribed scleroderma also had syphilis. An etiologic relationship could not be elicited, and the therapeutic test for syphilis did not offer relief for the scleroderma. The incidence of syphilis in cases of scleroderma is about the same as the general incidence of syphilis in other diseases.

A history of trauma was obtained in 11 of the 14 cases of scleroderma in bands. The most frequently observed site for this form of the disease is the upper extremity, with the history of an injury or blow to the corresponding shoulder or side of the neck. Other

instances of injury to the forearm, leg, or side of the head have been followed by the linear type of scleroderma. Trauma of practically all types has been suggested as etiologic factors in the disease.

Prognosis. The prognosis, as to cure, in cases of generalized scleroderma is poor. The protracted course of the disease is illustrated in our series by the fact that 26 patients (54 per cent) with generalized scleroderma had had the disease more than two years before they were seen at The Mayo Clinic. Of the 8 patients who died, the average duration of the disease was more than four years, with a maximum of twelve years and a minimum of one year.

Of the 48 patients with generalized scleroderma, the condition of 14.5 per cent was slightly improved, of 10.5 per cent decidedly improved, and of 6.3 per cent almost completely cured clinically. An analysis of the cases in which the patients recovered showed that the condition was of the edematous type of generalized scleroderma.

It is to be borne in mind that spontaneous remission is noted occasionally in the generalized forms and frequently in the circumscribed forms of the disease; this is a factor to be considered in the interpretation of the value of all types of treatment.

Acute systemic infections play a prominent part in the death of patients with generalized scleroderma, although cardiorenal insufficiency seemed to play the major part in our series of cases.

The prognosis in circumscribed scleroderma is good. There is nothing to indicate any serious sequelæ or severe constitutional symptoms. The outlook in respect to the changes of the skin, however, is not good; the resulting atrophy is permanent and of cosmetic concern. The progress of the circumscribed form of the disease is more readily controlled but usually it was arrested spontaneously with relatively little involvement of the skin. In young persons scleroderma in hands may cause deformities of one or more extremities which must be treated by orthopedic measures. Circumscribed scleroderma is essentially benign, affects the skin primarily, and is not associated with severe systemic disturbances.

Treatment. As has been indicated in considering the etiology of the disease, extracts of the thyroid gland have long been used in the treatment of scleroderma. In our series, the extracts were given in cases in which the basal metabolic rate was below the average. The preparations used were either thyroxine, 4 to 8 mg., or desiccated thyroid gland, 67 to 125 mg. The dosage of the drug was regulated to keep the basal metabolic rate between 0 and +10 per cent. The results of the use of the various preparations of the thyroid gland do not admit accurate tabulation or analysis because other therapeutic measures were undertaken simultaneously. The results of treatment with the preparations of the thyroid gland were disappointing in the group as a whole. In cases of hyperthyroidism, thyroidectomy was done without apparent change in the scleroderma and, likewise, the use of compound solution of iodine in the cases of

exophthalmic goiter resulted in improvement in the general symptoms but without effect on the scleroderma.

It is our belief that the value of extracts of the thyroid gland in the treatment of scleroderma is dependent not on the specific influence of the extract or the fact that the gland is manifesting hypofunction, but on the influence that the extracts exert on increasing the blood supply in the cutaneous vessels.

When arsenic was suspected of being a factor and in many other cases in which appreciable amounts of arsenic were found in the urine, sodium thiosulphate was given intravenously in repeated courses of 6 to 20 injections, but without noticeable improvement of the scleroderma.

Physiotherapeutic measures seemed to offer the outstanding symptomatic relief in this series. The treatment was of the simplest type consisting of ordinary baking followed by massage and active and passive exercise. Treatment by ultraviolet light seemed to be an adjuvant. The removal of unquestionable foci of infection was advised on general grounds.

When possible the patient was advised to move to a warm, sunny, dry, equable climate such as that of Arizona, New Mexico, Florida or southern California. A study of the returns from the follow-up letters would indicate that this was a major factor in the improvement of a large proportion of those who reported amelioration of symptoms. The patients in this series who showed the greatest improvement were those who moved to the warmer climate, who persisted faithfully in the use of dry heat locally, followed by massage and passive exercises, and who continued to take extract of the thyroid gland purely on empiric grounds.

Recently Adson and Brown made a preliminary report of the value of thoracic sympathetic ganglionectomy as a method of treatment for sclerodactylia. Observation and further experience with this method of treatment are necessary, although at this time it seems that the vascular type of sclerodactylia, the type in which the Raynaud syndrome predominates in the development of the scleroderma of the fingers, will show the most improvement following this operation.

Summary. A series of 48 cases of generalized scleroderma and 55 cases of circumscribed scleroderma was studied. In more than half of the cases of the generalized type, arthritis preceded or occurred simultaneously with the development of the scleroderma. In 33 per cent, the onset was preceded by varying degrees of vasomotor disease in the extremities. In addition, in the study of etiology, general infectious disease, such as influenza, or dysfunction of the glands of internal secretion, particularly of the thyroid gland, or arsenism, were observed. Sclerodactylia was observed in 89 per cent of these cases. The expectancy of life is difficult to determine, although seven years was the average length of life in this group, and symptomatic cure was obtained in 6 per cent only.

Morphea, or localized scleroderma, is a benign disease, whereas generalized scleroderma is a disabling and usually a fatal one. There is practically no parallelism between the two diseases in onset, course, clinical appearance, and prognosis, although the dermal changes are similar. Occasionally both diseases are present in the same patient.

Although the accumulated evidence does not contribute any established facts as to etiology, it warrants the belief that generalized scleroderma is the cutaneous manifestation of systemic disease in which changes in the vascular system play a leading part. The group in which the onset of the scleroderma seems definitely related to acute systemic infectious disease is offered symptomatic relief by medical and surgical treatment.

BIBLIOGRAPHY.

1. Adson, A. W., and Brown, G. E.: Thoracic and Lumbar Sympathetic Gangli-onectomy in Peripheral Vascular Diseases: Therapeutic Value, J. Am. Med. Assn. (In press.)
2. Alquier, L., and Touchard, P.: Lésions des glandes vasculaires sanguines dans deux cas de sclérodémie généralisée, Arch. de méd. expér. et d'anat. path., 1907, 19, 688.
3. Audry, C., and Chiatellier, L.: Sclérème des adultes et syphilis, Ann. de dermat. et de syph., 1923, 4, 1.
4. Ayres, S.: Scleroderma as a Possible Manifestation of Chronic Arsenic Poisoning, Arch. Dermat. and Syph., 1920, 2, 747.
5. Boardman, W. P.: Scleroderma with Special Reference to Its Etiology and Treatment, Arch. Dermat. and Syph., 1929, 19, 901.
6. Brooke, H. G., and Roberts, L.: The Action of Arsenic on the Skin as Observed in the Recent Epidemic of Arsenical Beer Poisoning, Brit. J. Dermat. and Syph., 1901, 13, 121.
7. Brown, G. E.: The Skin Capillaries in Raynaud's Disease, Arch. Int. Med., 1925, 35, 56.
8. Brown, G. E., and O'Leary, P. A.: Skin Capillaries in Scleroderma, Arch. Int. Med., 1925, 36, 73.
9. Castle, W. F.: The Endocrine Causation of Scleroderma Including Morphea, Brit. J. Dermat. and Syph., 1923, 25, 255.
10. Coekayne, E. A.: Congenital and Acquired Scleroderma in Childhood, Brit. J. Child. Dis., 1916, 13, 225.
11. Favier: Quoted by Castle.
12. Foerster, O. H.: The Relations of Internal Secretions to Cutaneous Disease, J. Cutan. Dis., 1916, 34, 1.
13. Gans, O.: Histologie der Hautkrankheiten, Berlin, J. Springer, 1925, p. 97.
14. Gitlow, S., and Steiner, S.: Scleroderma with Special Reference to the Blood Chemistry, Arch. Dermat. and Syph., 1924, 9, 549.
15. Golay, J.: Sur le rôle du système sympathique dans la pathogénie d'un grand nombre de dermatoses, Ann. de dermat. et de syph., 1922, 3, 567.
16. Goodman, H.: A Case of Scleroderma Diffusa in a Girl Nine Years of Age, J. Cutan. Dis., 1918, 36, 210.
17. Hektoen, L.: Diffuse Scleroderma Associated with Chronic Fibrous Changes in the Thyroid and Great Diminution in the Amount of Thyroidin; Increase in the Chromophile Cells and of the Colloid in the Hypophysis, J. Am. Med. Assn., 1897, 28, 1240.
18. Hutchinson, J.: On Morphea and Allied Conditions, Arch. Surg., 1895, 6, 350.
19. Hyde, J. N., and McEwen, E. L.: The Dermatoses Occurring in Exophthalmic Goiter, Am. J. Med. Sci., 1903, 125, 1000.
20. Knowles and Ludy: Scleroderma with Diabetes Mellitus Controlled by Insulin, Arch. Dermat. and Syph., 1926, 14, 613.

21. Kyrle, J.: Vorlesungen über Histo-biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, J. Springer, 1925, p. 137.
22. Lieberthal, D.: Sclerema Neonatorum and Scleroderma, J. Cutan. Dis., 1918, 36, 29.
23. Longeoe, W. T.: Hypoglycemia in Scleroderma; the Metabolism in Eight Cases with Reference to the Function of Glands of Internal Secretion, J. Am. Med. Assn., 1928, 90, 1.
24. Murray-Will, E.: Scleroderma and Syphilis, Brit. J. Dermat. and Syph., 1927, 39, 201.
25. Myers, C. N., Marples, E., Groehl, M., and Throne, B.: The Use of Sodium Thiosulphate in Diagnostic Procedure, J. Lab. and Clin. Med., 1926, 11, 836.
26. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin, for the Use of Students and Practitioners, 2d ed., Philadelphia, Lea & Febiger, 1921, p. 495.
27. Osborne, E. D.: Morphea Associated with Hemiatrophy of the Face, Arch. Dermat. and Syph., 1922, 6, 27.
28. Osler, W.: On Diffuse Scleroderma, with Special Reference to Diagnosis and to the Use of Thyroid Gland Extract, J. Cutan. Dis., 1898, 16, 49.
29. Osler, W., and McCrae, T.: The Principles and Practice of Medicine; Designed for the Use of Practitioners and Students of Medicine, 9th ed., New York, D. Appleton & Co., 1921, p. 1118.
30. Osterberg, A. E.: Personal communication.
31. Robinson, A. S.: Report of a Case of Scleroderma of the Skin, AM. J. MED. Sci., 1917, 154, 657.
32. Roques, E.: Le traitement opothérapique de la sclerodermie, Ann. de dermat. et de syph., 1910, 41, 383.
33. Scholefield, R. E., and Weber, F. P.: A Case of Sclerodactylia and Subcutaneous Calcareous Concretions, Brit. J. Dermat. and Syph., 1911, 23, 276.
34. Sequeira, J. H.: Four Cases of Scleroderma Associated with Disease of the Thyroid Gland, Brit. J. Dermat. and Syph., 1916, 28, 31.
35. Schulmann, E.: La syphilis des glandes endocrines, Paris méd., 1920, 35, 442.
36. Thibierge, G., and Weissenbach, R. J.: Concretions calcaires souscutanées et sclérodermie, Ann. de dermat. et de syph., 1911, 40, 129.
37. Throne, B., Van Dyck, L. S., Marples, E., and Myers, C. N.: Arsenic Findings in Dermatological Conditions, New York State J. Med., 1927, 27, 757.
38. Weidman, F. D., and Schaffer, L. W.: Calcification of the Skin, Including the Epiderm, in Connection with Extensive Bone Resorption, Arch. Dermat. and Syph., 1926, 14, 503.
39. Wise, F.: Acrodermatitis Chronica Atrophicans and Its Relation to Scleroderma, New York Med. J., 1923, 118, 73.

REVIEWS.

IMMUNITY IN INFECTIOUS DISEASES. By PROF. A. BESREDKA.
Pp. 364. Baltimore: The Williams & Wilkins Company, 1930.

IN this treatise, the author reviews various theories of immunity and attempts to clear up a number of misconceptions concerning the relations between virus and organism which are still circulating alongside facts solidly established. He points out that these relations vary not only with the nature of the germs, but very often with that of the cells which they invade. Recent acquisitions to the subject of immunity are presented in the form of "studies" which are more or less independent of one another but nevertheless form an integral whole and add greatly to our general knowledge of the subject of immunity.

The book comprises fifteen chapters, dealing with problems which include investigations concerning the bactericidal power of the leukocytes, bacterial hemolysins, microbial endotoxins, vaccination by various methods and the function of the skin in infection and immunity. In addition to reviewing the older theories of immunity, the author adds much to our knowledge of the subject with his theories and experimental evidence indicating that in the majority of affections, the cause of immunity seems to be more clearly bound up with the presence of antiviral in the region of receptive cells than that of antibodies in the blood. To quote the author: "Antiviral therapy—preventive or curative—founded upon the principle of local immunization without antibodies, has its position marked out in a number of morbid processes, which elude the action of serotherapy or of vaccine-therapy as they are practised today."

W. K.

LES SYNDROMES DOULOUREUX DE LA RÉGION ÉPIGASTRIQUE. Vols. I and II. By RENÉ A. GUTTMANN. Pp. 1140; 542 illustrations. Paris: Gaston Doin & Cie, 1930. Price, 200 francs.

THESE paper-bound volumes represent a critical study of the causes of pain in the epigastrium, made by an internist attached to Professor Gosset's Clinic. As Professor Gosset points out in his preface, the author has been able to make extensive clinical and radiologic studies and then to follow the patients to the operating

table where the exact pathology was exposed. The first chapter describes a definite method for the clinical study of epigastric pain in order to make it useful in leading to a diagnosis.

Various disease entities (ulcer, tumor, gall bladder disease, and so forth) producing pain in the epigastrium are then described separately and completely. No attempt is made to describe the etiology but the clinical signs and symptoms are given in considerable detail. Radiologic findings are well outlined and illustrated with very fine reproductions of typical films. Cases are briefly reported illustrating the text. The latter part of each section is devoted to a description of the treatment of the disease under consideration. The author gives first the treatment he usually employs and then a fairly complete résumé of the therapeutic measures described in the literature, the therapeutic point of view naturally differing in many respects from that of American authors. For example, in the treatment of cholelithiasis is given a list of the various springs and the pathologic conditions which may be benefited, such as, "Gall stones with relatively recent hepatic colic: Vitelle. Stones without recent hepatic colic: Vichy. Stones in obese patients: Brides-les-Bains, and so forth."

On the whole the work should prove most valuable to those interested in gastroenterology, the chapters on ulcer syndromes and the syndrome of the gall bladder standing out as especially well written.

L. F.

PROCEDURE IN EXAMINATION OF THE LUNGS. BY ARTHUR F. KRAETZER, M.D. 125 pages; 15 illustrations. New York: Oxford University Press, 1930. Price, \$2.00.

THOSE who teach physical examination of the chest will welcome Dr. Kraetzer's book as the opening gun on Fort Sumter. To students and physicians it will be a Bacdeker in a too often undiscovered country. The plan of the book is to present the method of approach to pulmonary diagnosis, showing how to elicit physical signs and when elicited how their true meaning should be induced. Beginning with a chapter on the "Actual Sounds," one is conducted through the hills and valleys of inspection, palpation and auscultation until the promised land of clear interpretation is reached. The chapter on "Diminished Breath Sounds" is the high point of the book. The desire of the author to eliminate Graeco-Latin terms from our chest parlance is excellent though not carried to its logical conclusion, and when he speaks of "the relative bronchiality of the apices," the Reviewer admits a complete bewilderment. Nevertheless, this is a book which will ease the path of student and teacher equally.

C.-F. L.

THE SCIENCE OF NUTRITION SIMPLIFIED. By D. D. ROSENWARNE, M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 314; 7 illustrations. St. Louis: C. V. Mosby Company. Price, \$3.50.

AFTER a brief discussion of the underlying principles of chemistry and physiology, the author presents clearly and simply the needs of the body for the various classes of food materials. The importance of eating a diet composed of a large number of foods is fully explained. There are, however, some statements the accuracy of which could be questioned. At the end of the book is inserted a table of food values.

The presentation of any scientific subject in a manner to be understandable by individuals untrained in science is always a difficult problem, and it is questionable if the author has entirely succeeded in this case. Nevertheless, anyone unfamiliar with the subject of nutrition could obtain many new ideas and facts by a study of this book.

J. J.

CLINICAL OBSTETRICS. By PAUL T. HARPER, PH.B., M.D., Sc.D., F.A.C.S. Pp. 629; 84 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$8.00.

THIS book describes the normal mechanism of labor and its conduct, with a discussion on obstetric analgesia, and then proceeds to a detailed presentation of the prominent abnormalities of pregnancy, labor and the puerperium, with a dissertation on the operative procedures that may be necessary for the various abnormalities mentioned. It is not a book for the undergraduate student: it presupposes a broad knowledge of the basic principles of obstetrics, and is unusually well suited to the needs of the general practitioner who is actively engaged in obstetrics, giving him a well-balanced description of the problems he may meet, an analysis of them, and a clear and concise method of attack. The personal element in such a manner of preparing a book of this nature may cause those whose lines of procedure are already well defined to probably object to the author's recommendations, but they are safe, sane and concisely expressed, and a comparison of methods hurts no one. Particularly was the Reviewer impressed with the presentation of the normal mechanism of labor, the discussion of the relative merits of version and high forceps in occiput posterior presentations, his sane attitude toward routine versions and his treatment of breech presentations, and the effort to show that toxemias of pregnancy need a rational therapy for the individual case and not a blind standardized set of orders. The illustrations are mostly line drawings but the correlation with the text is excellent. The book is highly recommended.

P. W.

HEMORRHOIDS, THE INJECTION TREATMENT AND PRURITUS ANI.
By LAWRENCE GOLDBACHER, M.D. Pp. 205; 31 illustrations.
Philadelphia: F. A. Davis Company, 1930. Price, \$3.50.

THE author advocates the treatment of internal hemorrhoids by the injection of 8 to 10 cc. of 5 per cent phenol in cottonseed oil. For thrombosed or external hemorrhoids surgery is indicated. No recurrences have been observed and there have been no ill effects from the injections. A special slotted anoscope has been devised to facilitate the technique. The method is painless and hospitalization of the patient is unnecessary. However, experience is essential to secure uniformly good results. A small series of cases of intractable pruritus ani have also been treated by injection. The results have been gratifying to the author.

The contents of this book might readily be condensed into one or two papers of average length by the omission of much repetition, needless summaries of short chapters and a series of unilluminating case reports. This verbosity, however, is the main fault. It is a clearly written, practical manual on a method of treatment which appears to have produced excellent results in the hands of an enthusiastic adherent.

E. E.

DISEASES TRANSMITTED FROM ANIMALS TO MAN. By THOMAS G. HULL, M.D. Pp. 350; 29 illustrations. Springfield, Ill.: Charles C. Thomas, 1930. Price, \$5.50.

THE preface states that "Diseases which may be transmitted from animals to man immediately concern—the veterinarian, the physician, the laboratorian and the health official—each—engaged with a different phase of the problem—and viewing it from a different angle." "The present volume was written with each of them in mind, to afford a common meeting ground where each might understand the problem of the other, and thus, through concerted effort reduce the number of infections which man contracts from animals."

The work is divided into five sections: I. Diseases of Domestic Animals and Birds—Tuberculosis, Anthrax, Foot and Mouth Disease, Malta Fever and Contagious Abortion, Milk-sickness, Actinomycosis, Smallpox and Cowpox, Glanders, Rabies, Psittacosis, Food Poisoning, Swine Erysipelas and Affections Caused by Animal Parasites. II. Rodent Affections—Plague, Tularemia, Spirochetal Jaundice, Rat-bite Fever, Rocky Mountain Spotted Fever. III. Human Diseases Spread by Animals—The Relations of Human Infections to Animals—Septic Sore Throat, Diphtheria, Scarlet Fever, Other Human Diseases Sometimes Contracted by Animals. IV. Animals as Passive Carriers of Disease Organisms—Botulism, Tetanus, Gas Gangrene. V. A Review of the Rôle

Played by Each Animal in the Spread of Disease—The Rôle of Cattle, Horses, Swine, Sheep, Goats, Dogs, Cats, Rats and Mice, Poultry, Birds and Wild Game. Then lengthy Bibliographical and General Indexes. There are also 29 illustrations, consisting of photographs and maps.

Each of the subjects is excellently and systematically treated, with a degree of conciseness and thoroughness that are rarely met together; the bibliographical references number well over 800, so that though the book is small it is almost encyclopedic in character, and can be most highly recommended. J. McF.

THE MECHANISM OF THE LARYNX. By V. E. NEGUS, M.S. (LOND.), F.R.C.S. (ENG.). Pp. 528; 160 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, \$13.50.

THIS book is really a noteworthy achievement representing the results of a decade of time-consuming and laborious investigation. The author has assembled thousands of facts, recorded the results of numerous experiments and stated his ideas, many of which are original and unique, in a most logical and convincing manner. Sir Arthur Keith, in his introduction, compares the author's methods to those of Hunter and Darwin. Every laryngologist, no matter how experienced, will have his horizon widened and his interest in the larynx stimulated by this book. The larynx is considered from all possible angles. The facts dealing with its evolution, comparative anatomy, responses to environment, and physiology, are sanely and clearly assembled. From the primitive larynx of Dipnoi the author traces laryngeal development to the highest mammals. The book is well organized and contains at the end of each chapter a conclusion and summary which aids greatly in crystallizing the facts already presented in detail. K. H.

BOOKS RECEIVED.

NEW BOOKS.

The Surgical Clinics of North America, Vol. 10, No. 2 (Chicago Number, April, 1930). Pp. 252; 72 illustrations. Philadelphia: W. B. Saunders Company, 1930.

The International Medical Annual, 1930. By Various Contributors. Edited by CAREY F. COOMBS, M.D., F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 508; 115 illustrations. New York: William Wood & Co., 1930. Price, \$6.00.

Preserves its usual high standard of wise selection and practical value.

*Tuberculosis Among Children.** By J. ARTHUR MYERS, PH.D., M.D., F.A.C.P. Pp. 208; 43 illustrations. Springfield, Ill.: Charles C. Thomas, 1930. Price, \$3.50.

The Morphine Habit and Its Painless Treatment. By G. LAUGHTON SCOTT, M.R.C.S., B.A. (OXON.). Pp. 94. London: H. K. Lewis & Co., Ltd., 1930. Price, 5/-.

"It is the object of this small volume to suggest that the psychic and somatic rehabilitation of the addict who commonly presents himself for treatment is a simpler and more hopeful task than it is credited to be; and that the avoidance of withdrawal-shock, to use the term in its widest sense, plays a more important part in the ultimate issue than is generally supposed."

*Gynecology for Nurses.** By GEORGE GELHORN, M.D., F.A.C.S. Pp. 275; 145 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$2.00.

I Fondamenti della Biotipologia Umana. By MARIO BARBÁRA. Pp. 122; 3 illustrations. Milano: Soc. An. Istituto Editoriale Scientifica, 1929.

Transactions of the American Otological Society, Inc., Vol. XIX. Pp. 217; 13 illustrations. New Bedford, Mass.: By the Society, 1929.

Síndrome de Oclusión Coronaria. By ANTONIO BATTRO. Pp. 214; 111 illustrations. Buenos Aires: Librería "El Ateneo," 1930.

Æsculapius. A One-act Play. By BARBARA RING. Pp. 40. Boston: Walter H. Baker Company, 1930.

An interesting item for Osler's Bibliotheca Literaria.

The Medical Directory of the National Medical Association of China, 1930, Second Biennial Issue. Issued on the Occasion of The Eighth Biennial Conference, February 2 to 8, 1930, Shanghai. Pp. 241.

NEW EDITIONS.

Varicose Veins. By H. O. MCPHEETERS, M.D., F.A.C.S. Pp. 233; 45 illustrations. Second edition. Philadelphia: F. A. Davis Company, 1930. Price, \$3.50.

Additions concerning the Trendelenburg and Bernstein tests, also a few modifications of the technique. The work is useful, as was the first edition, to those contemplating injection treatment of varicose veins.

Obstetrics for Nurses. By JOSEPH B. DELEE, A.M., M.D. Pp. 645; 269 illustrations. Ninth edition. Philadelphia: W. B. Saunders Company, 1930. Price, \$3.00.

"The type matter has been completely reset and the illustrations with few exceptions were done over" . . . "Emphasis has been placed on the care of confinement at the home of the patient."

Dental Formulary. By HERMAN PRINZ, A.M., D.D.S., M.D., Sc.D., D.M.D. (COLOGNE). Pp. 364. Philadelphia: Lea & Febiger, 1930.

"The complete exhaustion of the third edition of the *Dental Formulary* has necessitated a thorough revision of the entire subject matter. Many important additions have been made which may prove of interest to the dental practitioner and allied readers. Formulas which have lost their merit have been discarded, most of the new material has been added on solicitation of professional friends from all parts of the world."

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Gastric Secretion in Cancer of the Stomach.—POLLAND and BLOOMFIELD (*Bull. Johns Hopkins Hosp.*, 1930, 46, 307) write that satisfactory studies of the gastric secretions in carcinoma of the stomach have not been attained because of the presence in the hypomotile stomach of the products of stagnation, of blood or pus. The physician is confronted with a mixture of different substances which obscure completely the determination of the character of the gastric juice which the stomach is secreting. Their present study is made on a relatively small series of cases with cancer of the stomach (19 in all) who were observed in the hospital. They obviated the possibility of stagnant gastric contents being present by washing out the stomach for several days before the examination was done. The patient was starved for the preceding eighteen hours. A duodenal tube was introduced into the stomach, and the total secretions were withdrawn continuously over successive ten-minute periods. After two such periods histamin was injected and the gastric contents were gathered for from three to six further ten-minute intervals. The material that was obtained was studied grossly as to its quantity, the presence of acidity (titratability), the pH and ferment content. The authors report on their results somewhat as follows: Only a small amount of gastric secretion was removed. This was grossly abnormal in appearance. The typical material was made up of tenacious mucoid gray or brownish fluid, frankly bloody at times and in two instances foul. When there were normal acid values the juice was in no ways remarkable. The maximum quantity obtained was practically never over 10 cc., usually from 1 to 5 cc. There was usually an absence of titratability using the dimethyl indicator. Only three of the patients had figures approaching anywhere near the normal. In no instances were acid values above normal encountered by these authors in patients with cancer. The pH of the gastric contents tested colorimetrically in some instances showed

that traces of acid were being secreted, although the dimethyl test was negative. Five cases were tested for pepsin. In several instances, despite the fact that there was no free acid, pepsin was still demonstrable. The secretion of mucus was considerably reduced. The authors next considered the question of the cause of changes in the gastric secretion in cancer of the stomach, reviewing the literature to show how these changes have been explained by other observers. In summarizing their article, they lay stress on the deficiency of the gastric juice, as in no instance did they encounter acidity or volume of secretion above the average. They also make the statement that "all evidence points away from the occurrence of cancer in the previously normal stomach, although this may occur in a very small percentage of cases. Cancer appears to arise almost always on the basis of an already existing lesion, usually a chronic gastritis, less frequently a peptic ulcer."

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Postoperative Fat Necrosis of the Breast.—KING (*J. Coll. Surg. of Australasia*, 1929, 2, 233) says that Lec and Adir laid down certain criteria for its clinical diagnosis and its occurrence in an adipose breast, usually in an obese person, a history of trauma, painless and stony hardness of the mass, together with adherence to the skin without involvement of the deeper parts. A great deal has been said of the etiology of fat necrosis. Farr produced it experimentally by traumatizing the fat tissue of pigs and also suggested that the necrosis was due to the cutting off of the blood supply. Others consider that physical trauma was absent in some of their cases, and suggest that the exciting cause is the irritation of fatty material escaped from the ducts. Certainly fatty acid crystals and cholesterol crystals are found in sections, but these may arise from the fat tissue itself. There would seem, therefore, to be two degrees of change involving fat tissue in the breast: True traumatic fat necrosis, in which there is a history of injury, physical or otherwise, and in which death of fat tissue is demonstrable microscopically, and second, a chronic inflammatory condition associated with hyperplasia of the fat cells, the result of some irritant, but not associated with necrosis. It is, of course, problematical whether the term fat necrosis should be applied to such conditions. In all the cases of fat necrosis the pathologic changes may be analyzed into those that are the direct result of injury, the actual necrosis and those in which there is the reaction to the presence of fatty acids and cholesterol, which is secondary to the necrotic changes. This reaction is shown by the endothelial and fibroblastic proliferation, foreign body giant-cell formation and the accumulation of numerous small round cells.

Infusion Treatment of Postoperative Shock.—MACFEE and BOLD-
RIDGE (*Ann. Surg.*, 1930, 11, 329) state that the essential fact of shock
is de-oxygenation of the body tissues, whatever the absolute cause of
shock may be. De-oxygenation occurs from impairment of circulation.
The impairment of circulation results from diminution of blood volume
in circulation. This loss is due to stagnation of blood in the capillary
areas and to the escape of plasma from the capillary channels. Hemor-
rhage and dehydration are frequent factors. To rationally combat
shock restoration of volume of blood in effective circulation is of first
importance. Physiologic sodium chlorid solution has heretofore been
tried as a medium to replace lost volume and has been generally dis-
carded. By using physiologic sodium chlorid solution with or without
glucose in amounts much larger than have been employed, the authors
have consistently obtained gratifying results in the treatment of shock.
The danger of producing acute cardiac dilatation or pulmonary edema
has not been apparent in a relatively short series of cases. The authors
practise and urge, however, constant vigilance during the administration
of large amounts of solution. They believe that the results obtained to
date with this method of treatment warrant continuation of its use.

Cancer of the Prostate.—DOSSOR (*J. Urol.*, 1930, 23, 217) reports
that prostatic adenoma plays an important rôle in the pathogenesis of
numerous cancers; in 11.6 per cent of cases it undergoes malignant
transformation. Two types of prostatic cancer should be distinguished,
urethroprostatic adenoid cancer, which develops from the adenomatous
glands of the prostatic urethra and true cancer of the prostate which
develop from the prostate itself. The latter may coëxist with an
adenoma. Cancers and adenomata are associated in 58.7 per cent of
cases. Invasion of nearby organs and lymph glands always occurs in
cancer of the prostate. These extensions are very early, and before
they can be recognized clinically the cancer has extended widely past
the limits of the glands, and has invaded the pelvic and abdominal
lymph glands. Prostatectomy, radium therapy and radiotherapy have
only given very mediocre results, and cases remaining cured for more
than three years are the exception. True cases can only be obtained
in those patients operated upon with a diagnosis of adenoma, in whom
the histologic examination shows the existence of cancer. When cancer
has progressed sufficiently to be recognized it has, generally speaking,
extended widely. Therefore, it is prudent, at the present state of our
knowledge, to limit our efforts to palliative therapy, passage of sounds
and cystostomy.

Nongonorrheal Urethritis.—COSTELLANI (*Urol. and Cutan. Rev.*, 34,
147) claims that nongonorrheal urethrites are not of frequent occur-
rence, but it would appear from the author's observations that they are
not so exceedingly rare or nonexistent as some authorities would seem
inclined to believe. Nongonorrheal urethritis may be classified into
three groups, of traumatic origin, of protozoal and metazoal origin and
mycetic origin. Those of the first group are exceedingly rare, and from
a practical point of view may be omitted altogether. As regards the
second group, several of them are doubtful, the flagellates and some of
the other protozoa found probably not being true causative agents.

The urethrites of the third group are the most important from a practical point of view as there is little doubt that the fungi found are in a certain number of cases the true causative agents. But as in the case of so many other mycoses, there is a primary and secondary mycotic urethritis. Practically all the protozoa and fungi found in nongonorrheal urethrites of the male have been found also in cases of vaginitis and vulvovaginitis, and it is not, therefore, very improbable that in certain cases and under certain circumstances these affections may be transmitted by sexual intercourse as the author suggested some years ago.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

Preliminary Report on a New Local Anesthetic—Percain.—HÖFER (*Klin. Wchnschr.*, 1929, 8, 1249), reports in detail his experiences with the use of a new substitute for cocaine called percain in several hundred patients including a very wide variety of surgical conditions ranging from the most minor local operations up to extensive laparotomies for such conditions as carcinoma of the stomach, acute cholecystitis and the like. Throughout his entire experience the drug proved to be an exceptionally effective local anesthetic, its action being about twenty times as great as that of cocaine. It induces anesthesia with exceptional rapidity and its action is of high intensity and exceptionally prolonged, usually the anesthesia lasting for four to twelve hours. It has the disadvantage of producing a moderate to fairly pronounced degree of local vasodilatation which, however, is readily controlled by the addition of epinephrin to its solutions. No definite toxic effects were seen in the large series of observations but animal experiments proved it to be considerably more toxic than cocaine. Along with this increased toxicity and offsetting it, however, is its extraordinary degree of anesthetic potency. For subcutaneous infiltration anesthesia it is fully effective in 0.05 per cent solution which is similarly fully effective for infiltration of the deeper tissues. Its solutions in physiologic saline are easily prepared, can be boiled repeatedly without damage and can be kept for days or weeks without deterioration. For general and widespread infiltration in major operations from 50 to 150 cc. of such a solution are effective. At the time the solution is to be used 12 drops of 1 to 1000 epinephrin solution should be added for each 100 cc. The author warns against its use for splanchnic infiltration anesthesia, since in one instance this method of employment was followed by symptoms, which

might be regarded as due to intoxication. The drug itself is a synthetic, which differs entirely in its composition from other cocain substitutes, being the hydrochlorid of alfabutyloxyinchoninic acid diethylendiamid.

The Effect of Food and Other Substances on the Acid-base Equilibrium in the Human Body.—The rôle of diets in the treatment of diseases is continuously increasing. The significance of diet in therapy is due not only to its caloric content but to the chemical nature of both the organic and inorganic constituents. STRAUB (*Therap. d. Gegen.*, 1929, 70, 481) discusses the possibilities of influencing the acid-base equilibrium in man. The acid-base equilibrium is regulated with about 1000 times more exactness than the ion equilibrium in tissues. In this regulation the kidneys, intestines and to an even greater extent the lungs play prominent rôles. A disturbance of the normal acid-base balance is especially apt to occur in diseases of these organs. In case of renal insufficiency the acidosis is due largely to intermediary metabolites. Nevertheless, the acidosis can be influenced considerably by a milk vegetable diet with its rich base content. A patient with kidney disease can be shifted with relative ease into acidosis or alkalosis depending on the food chosen. It is so characteristic of impaired kidney function that the acid-base equilibrium can easily be influenced by outside factors, especially by food, that this condition is called "poikilopikrie." In the normal individual it is exceedingly difficult to change essentially the reaction of tissue fluids. The sensitivity of the acid-base regulation varies considerably in different species of animals. The regulation is rather incomplete in the rabbit and guinea pig, it is better developed in the dog, pig and cat, and is best in man. This is an important point to remember and commands caution in transferring conclusions obtained from animals to man. Whether food can influence the composition of tissue fluids in normal man is still an open question. Undoubtedly hormones, vitamins and radiating energy have a much greater influence than food and minerals on the mineral contents of tissues. The salt content of the body cannot be influenced essentially by the administration of sodium chlorid. Phosphoric acid, calcium and other inorganic compounds, whether administered orally or intravenously, leave the blood stream rapidly and their effect is fleeting unless they enter the blood stream continuously. After the administration of unbalanced diets the alkali reserve of the blood may show considerable change. Nevertheless, as a result of the compensatory influence of respiratory regulation, the reaction of the blood changes but little. The behavior of tissue fluids is unknown. A very strict diabetic diet may temporarily produce acidosis in normal individuals, but this effect disappears within a few days. In the problem of the capacity of various ions or inorganic compounds to change the acid-base equilibrium of the blood, the chemical reaction, ionization or molecular equivalent are not necessarily determining factors. As a matter of fact, certain neutral salts such as ammonium chlorid lend themselves best to producing changes in the alkali reserve of the blood. This is due to the fact that the ammonia is changed into urica and only the hydrochloric acid equivalent of the compound remains in the body. The understanding of the influence of other neutral salts is more difficult. Meat, cereals, cheese, egg,

artichoke and legumens are acid-forming foods in the human body. Milk, the majority of vegetables, and bulbous plants such as potatoes and most fruits deliver bases in the body. It is important to remember that the method of preparation may change the behavior of food substances in the body completely. The realization of this fact is of great practical significance in dietetics. The quantitative rôle of various food substances in mineral metabolism so far is not known and therefore tables containing the acid-base equivalents of food substances can be used only with reservation.

The Action of Atophan on Hepatic Excretion of Uric Acid.—Working under conditions of accurate control KÜRRI, (*Klin. Wchnschr.*, 1929, 8, 2239) studied the influence of atophan upon the elimination of uric acid through the bile in a group of 35 patients, among whom there were 8 with nephritis and one with orthostatic albuminuria. He administered 3 doses per day of 1 gram each of atophan by mouth to half of these and to the other half he gave $\frac{1}{2}$ gram of sodium atophan intravenously just before the removal of the bile by the duodenal tube. These experiments show that in the majority of patients without renal disturbance both the oral and the intravenous administration of atophan increases the elimination of uric acid in the bile by from 30 to 50 per cent. In the group having renal disturbance the increase in elimination of uric acid is always much greater, ranging from 60 to slightly more than 125 per cent. The author concludes that the liver plays an important part in the reaction of purin metabolism and that, next to the kidneys, it is the most important organ for the elimination of uric acid. In the course of his study he also observed that the administration of atophan was followed by an increase in the daily excretion of bile, amounting to about 120 per cent.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Cisterna Magna Pressure Syndrome.—RUBEN and CHASNOFF (*Arch. Pediat.*, 1930, 47, 201) describe a syndrome which occurs in the course of meningitis. This consists of rapid pulse, rapid respiration, a high or a low temperature and occasional delirium. They feel that it is due to pressure on the medulla and the pons by a distended cisterna. In cases due to pressure on the medulla, cisternal tap produces immediate improvement in the general condition. They advise against the introduction of serum at the first tap regardless of the character of the removed fluid. In several of their cases there was no need for further tapping. The symptoms are usually due to pressure and not to infection or toxemia. If symptoms should return, a second tap should be performed and if the fluid withdrawn is turbid and if the previous exami-

nation reveal organisms, serum should be introduced but not in larger quantities than one-half of the fluid removed. This procedure is advised even if fluid can be obtained by lumbar puncture, if the syndrome is present. In these cases the cisterna is apparently not in direct communication with the rest of the subarachnoid space so that lumbar puncture does not relieve distention of the cisterna. If this syndrome is allowed to remain without relief for as long as a week the outcome is invariably fatal.

The Blood Platelets in Newborn Infants.—JARCHO (*Arch. Pediat.*, 1930, 47, 230) studied a series of 100 cases and found that the blood-platelet counts in normal newborn infants showed wide variations. In his series the variation was from 78,740 to 500,000 with the count in the majority of cases between 150,000 and 250,000. As a rule the platelet count is lower in newborn infants and during the first few days of life than in older children and adults. Relatively low platelet counts in newborn infants are not associated with prolonged coagulation or bleeding time except at the level of 60,000 at which point hemorrhagic symptoms may develop. There did not seem to be any definite correlation between the red-cell count and the platelet count. Not only may the total number of platelets be important but there may be qualitative changes in the platelets themselves.

Comparative Value of Viosterol and Cod-liver Oil as Prophylactic Antirachitic Agents.—DESANCTIS and CRAIG (*J. Am. Med. Assn.*, 1930, 94, 1285) found that cod-liver oil in a dosage of three teaspoonsful daily prevented rickets in 97 of 100 cases studied. Viosterol given in a dosage of 10 drops daily prevented rickets in 77 per cent of 123 cases studied. Of the patients in this series 23 per cent developed clinical signs of rickets. Many writers have reported in large series that infants receiving no antirachitic agent at all developed signs of clinical rickets in about 25 per cent of cases. From this it would seem that viosterol given in dosages recommended by its various manufacturers is less effective in the prevention of rickets than is cod-liver oil. In the cases reported in this study the infants on viosterol received about twice as many rat units of vitamin D as those on cod-liver oil. From this it would seem that either the present recommended prophylactic dose of viosterol is too small to prevent rickets or that rickets is not due entirely to a deficiency of vitamin D. Of these two inferences, the latter seems more probable.

Asthma in Children.—PESHKIN (*Am. J. Dis. Child.*, 1930, 39, 774) found in a series of 425 cases of asthma that the asthma remained severe, persistent and of long duration in spite of intensive modern treatment in 41 children ranging in age from two to fourteen years or approximately 10 per cent of the series. Twenty-five children, 22 of whom were sensitive and 3 of whom were nonsensitive to protein were treated by a change of environment. In spite of the fact that the inhalant and dietetic restrictions were kept less rigid than at home, 23 or 92 per cent were markedly improved or entirely relieved of asthma. Seventeen of these 25 children were returned to their homes for periods varying from six months to five years or an average of two years per patient. Thirteen

of these 17 children or 76 per cent are now greatly improved or entirely relieved from asthma. In some of these children appropriate treatment after change of environment was successful whereas it had failed before. Sixteen of the 41 children were not treated by a change of environment because of the lack of facilities and other reasons and have been used for comparison as a control. They all have continued to suffer from chronic asthma. Allergy of itself cannot be explained entirely on the basis of protein sensitization because the sensitizing substances in themselves are merely excitants and not the basic cause of the symptoms. A patient in the state of physiochemical equilibrium will enjoy freedom from symptoms in spite of exposure to exciting substances. If any factor overthrows this governing mechanism symptoms will appear. Such factors may be either specific or nonspecific or both. It is emphasized that an appreciation of this fact will aid in establishing a clearer conception of asthma and will lay the foundation of a more intelligent management of this disease in childhood. When the physiochemical imbalance has been greatly disturbed the various specific and nonspecific factors always induce asthma even though the patient is receiving appropriate treatment at the time. In these cases there is little that can be done to give relief until Nature itself restores the physiochemical equilibrium. It has been found that a change of environment preferably a home prepared to accommodate allergic patients, was of definite value in partially or completely restoring the physiochemical balance. Until newer methods of treatment are advanced with which to successfully control or free this group of children from asthma the establishment of homes where a child with chronic refractory asthma can be kept for at least six months is a very urgent humane and economic necessity as well as a therapeutic measure of definite value.

Submucous Fibrosis of the Bladder Outlet in Infancy and Childhood.
—CAMPBELL (*J. Am. Med. Assn.*, 1930, 94, 1373) states that this condition is not an uncommon condition but its recognition in the past has been extremely rare. They found that girls were less likely to have this condition than boys. Pathologically the lesion is a submucous sclerosis of the vesical orifice. The internal sphincteric mechanism may be partially but is never involved completely in the scar. Sphincteric function is interfered with giving rise to urinary obstruction associated with incomplete or difficult bladder emptying. The pathology of the urinary tract are those of infravesical obstruction and may result in renal injury. Symptomatically the lesion is evidenced by urinary frequency and difficulty, dysuria or dribbling as well as by various degrees of chronic bladder retention. Systemic symptoms when present are manifestations of uremia and are referable both to the gastrointestinal tract and the central nervous system. Infection usually is present and is the cause of a low-grade fever. The history and cystography suggest the diagnosis and cystoscopy confirms it. The treatment is surgical and consists of removal of the fibrotic mass. It is necessary to observe the same pre-operative preparation and postoperative care as for prostatectomy. Under proper conditions a satisfactory surgical outcome should be expected. The recognition and treatment of this condition early may prevent serious and fatal renal disease in later years.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

R. L. GILMAN, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Bismuth Arsphenamin Sulphonat (Bismarsen) in the Treatment of Syphilis and Other Spirochete Infections.—KOLMER (*Arch. Dermat. and Syphilol.*, 1930 21, 394). Bismarsen, representing a combination of two such well-known spirocheticidal agents as arsphenamin and bismuth (arsenic 12 to 15 per cent, bismuth, 23 to 25 per cent) is a distinct advance in the chemotherapy of syphilis. Kolmer reviews the work of Stokes and Chambers, O'Leary and Tobias and details his results in the experimental and clinical evaluation of Bismarsen. The feature of intramuscular administration is not only of frequent technical advantage but is of importance where slower absorption and slower elimination are necessary. Representing combination therapy as it does, it possesses the summation and synergistic effects of both drugs. Bismarsen is water soluble, rapidly diffused from the site of injection as shown by roentgenograms, and is of low toxicity in the ordinary dose of 0.2 gm. In the experimental animal, only after prolonged administration of Bismarsen in doses of 0.003 gm. per kg., occasional histologic changes were noted in the kidney. It is tolerated intravenously in the experimental animal about ten times less than that of the intramuscular route, comparable to mercurochrome and flumerin. The intravenous route is not advisable clinically, although *in vitro* Bismarsen produces neither hemolysis nor agglutination. The local reaction is usually more than bismuth in oil and usually less than of mercury salicylate or sulpharsphenamin. The use of butyn-water as a solvent has reduced the incidence of immediate discomfort but has not prevented the occurrence of a possible later local reaction. The occurrence of constitutional reactions has been low in the author's experience (800 injections), but has included hepatitis with jaundice, pruritus, tingling of fingers and toes and the "nitritoid" reaction. No hemorrhagic encephalitis or purpura with aplastic anemia has been observed, and no severe gastrointestinal reactions, gingivitis or stomatitis occurred. Albuminuria with casts was rare. Bismarsen possesses trypanocidal effects on the rat to a well-marked degree. Its spirocheticidal properties in rabbit syphilis may be expressed by a comparison of its minimum single curative dose intravenously to that of arsphenamin, that is, 0.015 gm. per kg. as compared to 0.014 gm. per kg. Intramuscularly in the rabbit it produces a slower disappearance of spirochetes and healing of the testicular lesions than arsphenamin intravenously, but

it is equal or superior to bismuth or sulpharsphenamin intramuscularly. In human syphilis the average time for disappearance of spirochetes from the initial lesion was found to be seventy hours. (Stokes and Chambers found twenty-nine hours, O'Leary seventy-five hours.) The solution of Bismarsen in butyn-water possesses marked bactericidal properties on *Staphylococcus aureus* and hemolytic and nonhemolytic streptococci. Clinically, Kolmer used Bismarsen in 4 cases of seronegative primary syphilis. His plan included the administration of Bismarsen every five to seven days for a course of 10 injections. After four courses and following observation of from eleven months to three and a half years there have been no serologic or clinical relapses or spinal fluid changes. Similar results occurred in 7 cases of secondary syphilis. Kolmer concludes, however, that Bismarsen, because of its slower action, is less superior to arsphenamin in acute early syphilis. In latent or chronic syphilis, Bismarsen appears to its greatest advantage as (1) an intramuscular preparation of slower absorption it tends to eliminate the occurrence of a possible disastrous Jarisch-Herxheimer reaction; (2) a safer agent in testing a patient's tolerance to arsenic either after a long rest period or a previous constitutional reaction; (3) yielding good tonic effects so important in chronic syphilis, particularly *tabes dorsalis*; (4) representative of an ideal combination therapy for Wassermann-fast cases. It has not caused the rapid healing of late external lesions, but has afforded gradual relief from lightning pains and the headaches of syphilitic meningitis. Bismarsen was found successful in congenital syphilis, particularly for its good effect on interstitial keratitis and general tonic effects. It has not succeeded generally in completely reversing the Wassermann in these cases. Its technical advantages in young children are obvious. Finally, the author found the intramuscular use of Bismarsen valuable in 2 cases of pulmonary spirochetosis and in 6 cases of Vincent's angina.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Röntgen Treatment of Uterine Fibroids.—According to Wood (*J. Am. Med. Assn.*, 1930, 94, 601) a large number of patients with uterine fibroids are still being operated upon who could obtain relief from their symptoms by a method which is less dangerous to life, simpler of application and, in properly selected patients, just as effective as surgical removal with practically no mortality. His opinion is based upon 200

cases of his own which have been carefully observed. In balancing the results of the two types of treatment it is apparent that the advantages of surgery are the certainty of removal of the tumor, the possibility of avoiding sterilization in young women and the possibility of handling other pathologic conditions at the same time. Against surgery may be placed the mortality, even though low; the fact that the patient is unfit for work for at least a month, the necessary expense incident to such treatment and the disadvantages of an abdominal scar with the occasional keloid hypertrophy or ventral hernia. On the side of irradiation, radium being considered first, the advantages are that most fibroids will shrink considerably or even disappear with a single treatment of 1500 mg. hours. Menstruation may reappear after a short period of amenorrhea, in which case the patient may later become pregnant. The disadvantages of radium are that it necessitates hospitalization, the mucous membrane in contact with the radium is apt to become atrophic later or an actual constriction of the cervix with pyometra may follow, while the postirradiation sickness may be just as serious as that following surgical removal. The expense of radium is also considerable. The advantages of Roentgen treatment are that the patient is ambulant; the treatments are infrequent, being one or two weeks apart; they are short, being not over twenty minutes each; the patient as a rule does not suffer from any postirradiation symptoms; the radiation action is chiefly on the ovaries, and there is no caustic effect on the endometrium. As is well known, patients between twenty-five and forty years of age as a rule require slightly heavier dosage than those older than forty years. The reduction of a fibroid in a young woman by Roentgen irradiation without the production of permanent amenorrhea is a difficult matter and myomectomy is preferable in such instances. With modern feminine costumes, the radiation can be given without the patients having to undress which is a great saving of time for patient and operator. After the second or third dose the skin over the abdomen and back is examined to see that there is no reddening; otherwise it is entirely unnecessary to strip such patients. The patient is rarely detained more than twenty-five minutes, an important factor for those whose business or household duties make it imperative to conserve time. (A pre-irradiation curettage and histologic examination of the curettings should be invariably performed when employing either radium or Roentgen ray, in order to exclude the possibility of pregnancy or fundal carcinoma—C. C. Norris.) Neurotic patients should be told that the menstruation subsequent to the first treatments may be accentuated. It is always necessary to warn the patient about not getting sunburned or having ultraviolet ray treatment, as no matter where this sunburn is, the family physician not infrequently considers it an irradiation burn and so informs the patient. Such information greatly increases the difficulty of handling the patient and may result in threats of lawsuits or other annoyances to the radiologist, especially among the more ignorant type of patient. A study of Wood's records shows that in about 90 per cent of the private patients without complications receiving a complete series of treatments, a satisfactory clinical cure was obtained. In more than half of these there are records that there is no evidence of fibroma being present, while in the others the tumor has almost disappeared. In the dispen-

sary type of patient the results are even better because all these women desire is to be relieved of the bleeding or extreme pressure symptoms so that there are clinically fewer failures in this group than in the more highly sensitive type.

Endometrial Cysts of the Ovary.—In this country there is so much enthusiasm over Sampson's theory of endometrial ovarian cysts that it is possible that the pendulum has swung a bit too far in calling certain cysts "endometrial," when in truth they are of a different etiology. Concerning this point a mild protest has been presented by KING (*Surg., Gynec. and Obst.*, 1930, 50, 1) of Melbourne, Australia. He states that endometrial cysts of the ovary and tarry luteal cysts possess many features in common and are indistinguishable macroscopically. Microscopically, the diagnosis requires careful study because the epithelium in both cases may be similar, the subjacent stroma in the luteal cyst may closely resemble that of endometrial glands, gland spaces may be seen in both, pseudoxanthomatous cells occur in both and the characteristic structure of the luteal cyst may not be apparent in all parts of the wall. Their similarity extends to their physiology and complications. Tarry luteal cysts sometimes rupture into the peritoneal cavity, thus producing secondary blood cysts and a severe inflammatory reaction similar to that produced by endometrial cysts. His experience suggests that the endometrial diagnosis has been made too frequently and on insufficient evidence or erroneous interpretation. The frequency with which he is able to demonstrate a luteal nature for cysts of this kind suggests that many of those recorded are possibly luteal in origin.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Gas Bubbles in the Anterior Chamber—A New Differential Diagnostic Sign of Metastatic Bacillus Coli Enophthalmitis in Diabetes.

—There are in the literature a few cases in which a metastatic Bacillus coli infection has occurred in the eye. In only one of these, however, was this complicated with diabetes. None showed gas formation. REIS (*Klin. Monatsbl. f. Augenh.*, 1929, 83, 784) reports a case in which a diabetic had a severe renal infection with Bacillus coli. Five days before death the left eye was sightless, there was pain and iridocyclitis with occlusion of the pupil. The following day there was an hypopyon. The day after Reis saw the patient for the second time; the condition of the eye then raised the suspicion of a metastatic panophthalmitis. The pupil did not dilate with atropin, the anterior chamber was very shallow. Between the iris and the cornea a few discrete gas bubbles could be plainly seen. The eyeball was not injured, nothing had been removed from the anterior chamber nor had there been any other intervention. Unfortunately it was impossible to do a bacteriological

examination after death. Three cases of gas-forming panophthalmitis are reported in the literature. In all three, however, there had been an injury to the eye. The finding of gas, which has not hitherto been observed in metastatic coli enophthalmia would indicate that the infectious agent was the same as that in the renal disease—*Bacillus coli*. The bacillus found favorable conditions in the eye, a nutrient medium containing sugar due to the presence of diabetes, and these conditions must have led to the development of gas, to the formation of gas bubbles. The finding of gas bubbles in the anterior chamber could thus be advanced in differential diagnosis of metastatic panophthalmus—the positive proof of gas bubbles should warrant the diagnosis of metastatic coli infection. This attempt at explanation is all the more probable since it has been shown that the vitreous is a good medium for *Bacillus coli*.

The Blood-sugar Content of Cataract Patients.—Because of the frequent relation between the endocrine glands and cataract, for example, diabetic cataract, the question has been raised whether senile changes in the pancreas causing an increase in the blood-sugar level may not play a rôle in the development of senile cataract, even though diabetes is not present clinically. Attempts to substantiate this by blood-sugar determinations on cataract patients have been reported in the American and the Russian literature with very contradictory results. MEHLHOSE (*Klin. Monatsbl. f. Augenh.*, 1929, 83, 97) checked these results on 50 hospitalized patients with senile cataract, chosen with only one requirement—that the urine be sugar-free. The blood-sugar level was found to be above the upper limit of normal in only 3 patients (6 per cent). The sugar tolerance was tested in 10 patients and found to be normal. While the number of patients examined was small, Mehlhose believes that an increase in the blood-sugar level in nondiabetic patients with senile cataract is relatively rare and that the tolerance for grape sugar appears to be normal. At least an increase in blood-sugar level and a lowered sugar tolerance can scarcely be an important etiologic factor in gray senile cataract. Therefore an antidiabetic diet would scarcely halt its development.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

The Function of the Muscular Attachments of the Tonsil.—The effect upon the tonsil, particularly with reference to the rôle that the muscular attachments play in its function, apparently is little understood. Following a detailed description of the structural, muscular and neural anatomy of the tonsil, TROTTER (*Ann. Otol., Rhinol. and Laryngol.*, 1929, 38, 825) presents the results of certain experiments

designed to ascertain the degree of muscular pressure exerted on the tonsil during the act of deglutition, gagging, and retching. It was observed that stimulation of the nerve endings in the mucosa of the fauces, pharynx, and tonsil causes a reflex action which affects the peritonsillar muscles. By the conjoined and simultaneous contraction of the muscles at the upper pole, the palatoglossus and palatopharyngeus muscles, and the tonsillopharyngeus muscle,¹ as well by the traction of the plica semilunaris, a series of mechanical displacements and eversion of the organ occurs, producing an expelling action or disgorgement of the tonsillar pouches and crypts. By this method the tonsillar crypts are freed of foreign material.

The Bárány Symptom Complex.—In calling attention to certain outstanding characteristics of the Bárány syndrome—such as bilaterality of involvement, absence of labyrinthine response to caloric stimulation, abnormalities of past pointing at the shoulder but not at the wrist, and pyrexia, RATNER (*Zentralbl. f. Hals-, Nasen-, u. Ohrenh.*, 1929, 14, 263) cites the case of a twenty-one-year-old female suffering from bilateral tinnitus, auditory hyperesthesia and postauricular pain in whom there were bilateral mastoidal tenderness, altered caloric reactions, spontaneous past pointing and a continued pyrexia state. The author localizes the lesion to the cerebellopontine angle with involvement of N. V and N. VIII.

A Research on Blood Groups and Otosclerosis.—JANNUZZI (*Arch. ital. di otol.*, 1929, 40, 499) determined the blood groupings of all the available members of five families, in each of which several persons—deaf from otosclerosis—occurred. It was ascertained that all the deaf members of a given family belonged to the same blood group. In one family all were in Group II; in another, all were in Group IV, and in the remaining three, all were in Group III. The author interprets his results as confirming the idea of an hereditary tendency in otosclerosis rather than as suggesting a possible connection with any particular blood group.

Concerning the Indications for Opening the Mastoid Process in Cases of Acute Suppurative Otitis Media, with Especial Reference to the Question of Early Operation.—From his experiences in 784 cases, HAYMANN (*München. med. Wchnschr.*, 1929, 76, 947) has concluded: (1) That surgical intervention within the first fortnight is rarely necessary; (2) that the indications which have been promulgated by the sponsors of mastoidectomy early in the course of otitis media do not always warrant operations, and (3) that whereas early surgical interference of the mastoid process is not often a dangerous procedure, *per se*, by the same token it carries with it no guaranteed protection against subsequent complications. Inasmuch as the clinical application of his views has yielded cures in over 98 per cent of his cases, the author feels justified in pursuing his policy against premature mastoidal operations until such time as convincingly better results can be proven by adequate clinical materials.

¹ Fowler and Todd: Vide Retrospect: The Muscular Attachments of the Tonsil, AM. J. MED. SCI., 1928, 176, 748.

RETROSPECTOR'S NOTE.—The retrospector is entirely in accord with this policy, advocating the conservative management of these cases and abstention from often unnecessary operations not only in practically all cases of acute suppurative otitis media but also in a large percentage of those presenting evidences of mastoidal involvement. While admitting the remote possibility of the exploited "sin of omission," he has yet to regret, in a single instance, having chosen not to subject a patient to mastoidectomy until the clinical, hematologic and roentgenologic findings indicated, incontrovertibly, its necessity and expediency.

Some Remarks on Deafness of Focal Infective Origin.—MACKENZIE (*Zentralbl. f. Hals-, Nasen-, u. Ohrenh.*, 1929, 14, 262) attributes to focal infection more cases of progressive deafness than all other causes combined and eight times more instances of nerve deafness than syphilis. As frequently indicative of an infective focus is an unilateral labyrinthine involvement—often with vestibular manifestations, particularly vertigo. The inflammatory lesion may result either from the bacteria *per se* or their toxins and may be borne to the inner ear *via* blood stream or lymphatics. The importance of an exhaustive search for all possible foci of infection is emphasized—as is the necessity of their removal. It is pointed out that, in the last analysis, improvement of audition and disappearance of dizziness should follow the eradication of all demonstrable infective foci—if they are the sole etiologic factors.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

Intravenous Urography by Means of Uroselectan.—In 1923 Osborne, Sutherland, Scholl, and Rowntree were the first to attempt the visualization of the urinary tract by intravenous injection of a 10 per cent solution of sodium iodid. Similar experiments were made subsequently by Rosenstein, von Lichtenberg and others. Later a synthetic compound, selectan neutral, was developed by Bing and Roth and tried by von Lichtenberg in his urologic service. This proving to be more or less toxic, Bing and Roth modified the original compound and finally obtained uroselectan, which has been employed by von Lichtenberg with a marked degree of success. Recently SWICK (*Am. J. Surg.*, 1930, 8, 405) has tried uroselectan with equally good results. Uroselectan is nontoxic, very soluble in water, neutral in reaction, and under normal conditions excreted as such through the genitourinary tract of 80 or 90 per cent within eight hours. For an adult dose, 33 to 40 gm. is dissolved

in doubly distilled water to a volume of 100 cc. filtered and sterilized in a water bath or autoclave. Injection is made with a syringe in two stages, five minutes apart. The first examination with the Roentgen ray is made fifteen minutes after injection, a second twenty or thirty minutes later, and a third also at the latter interval. Films are also exposed at two-to four-hour intervals afterward as necessary. During injection patients experience thirst and a sense of generalized warmth. Transient nausea or vomiting may occur. It appears, however, that uroselectan is well-tolerated for intravenous pyelography and yields practical results. It has a field of application wherever ureteral catheterization is dangerous or impossible, or where mechanical or infectious factors prohibit instrumentation. In the presence of bleeding, in cases of implanted ureters, and in children, the clinical advantage of the method is obvious. Some excellent pyelograms are shown in the illustrations accompanying Swick's article. Discussing Swick's paper, Beer considered it evident that with uroselectan in the future the general practitioner with the aid of the radiologist will be able to make periodic health controls of his patients which will be accurate without relying on urinalyses and palpation. In this way, lesions of a surgical character in kidneys, ureter and bladders will be spotted at a much earlier period than at present when many patients and physicians still dread cystoscopic pyelography. Excellent shadows are obtained in hydronephrosis, in ureteral stone, kidney stone and other mildly obstructive conditions with fair renal function. Hyman also discussed Swick's paper and stated that the kidney shadow is more intense than in the ordinary pyelogram, although in general the pelvis and ureter are not as distinctly outlined as they are with retrograde pyelography. With obstruction of the ureter or pelvis the intravenous pyelogram is more intense than in nonobstructive conditions.

Intranasal Ultraviolet Irradiation in Nasal Accessory Sinus Diseases.—REAVES (*Arch. Phys. Therap., Roentgen Ray and Rad.*, 1929, 10, 488) has found that ultraviolet rays applied intranasally will abort common colds if used during the first twelve or twenty-four hours after the onset, and that they are of value in acute sinus infection and mild cases of ethmoid sinusitis in particular. In the more advanced types of chronic sinusitis it is his custom to operate and follow up with irradiation after three or four days. In atrophic rhinitis the intranasal application of ultraviolet rays helps to clear up the scabs and odor by improving the condition of the mucosa. Applications require from one to one and a half minutes, gradually increasing to three minutes, and are made daily if necessary.

Electrocoagulation of Tonsils.—Although not condemning tonsillectomy, DOANE (*Arch. Phys. Therap., Roentgen Ray and Rad.*, 1929, 10, 495) prefers electrocoagulation on account of its comparative safety and because many patients who need tonsillectomy will not submit to a cutting operation. Electrocoagulation methods, he considers, avert danger from hemorrhage or mutilation. Age is no contraindication. Special instruction in the procedure is necessary. Among the various methods, the author has a preference for the bipolar high-frequency current.

Roentgenologic Studies of the Mastoid in Infants.—After the age of six months a cavity having the shape of the mastoid can be demonstrated below the tegmen tympani and behind the external auditory meatus in good roentgenograms, according to MARTIN (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 431). This cavity varies markedly in size and may measure $\frac{3}{4}$ inch in diameter and show definite cell structure by nine months, although such excessive development is unusual. Diploetic mastoids are probably diploetic from the start, whereas cellular mastoids begin as large single cavities, which slowly increase in size and usually begin to show cellular structure at nine to sixteen months. The presence of pathologic conditions of the mastoid can usually be detected in good roentgenograms after the age of six months, though double infections often make interpretation difficult.

Zinc Ionization in the Treatment of Intumescent Rhinitis.—The broad indication for intranasal ionization is intumescent or early hypertrophic rhinitis, according to GALE (*Arch. Phys. Therap., Roent. Ray and Rad.*, 1929, 10, 486) and his results have been favorable. The method consists of packing the side of the nose to be treated with long, narrow strips of gauze saturated in a weak zinc solution. This solution is made of 1 per cent, or less, of zinc sulphate and distilled water to which a very small amount of glycerin has been added. After the packing, a zinc or copper wire is inserted into it and connected with the positive terminal of a galvanic apparatus or battery cells. The indifferent electrode, which is made of a moist pad, is applied to the forearm or other body surface, and connected to the negative terminal. The current is now turned on. From 3 to 10 ma. of current are tolerated comfortably by the average patient. The treatment consumes about fifteen to twenty minutes. The patient will complain of a metallic taste and temporary salivation, but no other disagreeable symptoms. After the packing is removed, a white coating may be observed on the turbinates and septal membranes. After twenty-four hours the membranes present a grayish appearance and a day or so later a definite shrinkage is observed. The turbinates lose their boggiess and approach a normal tendency. All untoward symptoms disappear in three days. Improved ventilation and drainage are the direct result. Only occasionally is it necessary to repeat the treatment. If a second treatment is necessary it should not be given in less than ten days to two weeks.

Nontraumatic Diaphragmatic Hernia.—Seven cases of diaphragmatic hernia are reported briefly by ELWARD and OTELL (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 535). In every case save one a portion of the stomach had herniated through the esophageal hiatus, and the condition was demonstrable with the Roentgen ray. The hiatus is practically a slit in the muscular portion of the diaphragm, which happens to be the most easily distensible portion of the structure. The history of these cases not infrequently shows a more or less protracted period of transient increases of intraabdominal pressure, such as would result from the violent coughing in pertussis or chronic bronchitis, straining at stool,

or the second stage of labor, and one can understand why herniation in this area should occur. Clinically, the picture presents a right upper quadrant syndrome, simulating cholecystitis, or gastric or duodenal ulcer. The most constant symptoms are pain in the epigastrium, regurgitation and abdominal distress on assuming a recumbent position. The diagnosis can be made with certainty only by means of the Roentgen ray, carefully studying the lower esophagus with the patient in various positions. Distinction must be made from cardioesophageal relaxation, diverticulum of the lower end of the esophagus, diverticulum of the stomach, cardiospasm, hour-glass stomach, cancer, perforation of the esophagus and congenitally short esophagus.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

The Cerebral Circulation.—WOLFF (*Arch. Neurol. and Psychiat.*, 1929, 22, 686) reports on the action of acetylcholine, the extract of the posterior lobe of the pituitary gland, and amyl nitrite on the cerebral circulation, in three separate articles. The method consists of observation by means of a microscope, through a window in a trephine opening in the skull. With acetylcholine injected intravenously he found dilatation of cerebral arteries, veins and minute vessels with usually a rise in cerebrospinal fluid pressure and a fall in systemic arterial pressure, and is able to show that the chemical content of the blood has more effect in regulating the diameter of cerebral bloodvessels than its hydrostatic pressure. Extract of the posterior lobe of the pituitary gland caused constriction of pial arteries, arterioles and minute vessels, again showing the effect of the chemical content of the blood. With amyl nitrite he found a dilatation of cerebral vessels with a fall in systolic arterial pressure and rise in cerebrospinal fluid pressure. The experiments were conducted on cats.

Malaria as a Therapeutic Agent for Paresis.—DE ASIS (*Arch. Neurol. and Psychiat.*, 1929, 22, 752) reports on 101 cases treated in the Worcester State Hospital with benign tertian malaria. He finds no apparent relationship between the clinical results of treatment and the number of paroxysms and his only criterion for deciding how many chills a patient may have is his general condition, except that not more than 18 paroxysms are allowed in a given case. He terminates the malaria by quinine administered by mouth and cautions against its intravenous use. Complications during the treatment were herpes labialis, jaundice

cachexia and anemia, 2 cases of ruptured spleen and one of cerebral hemorrhage and edema. Serologically he finds few changes in either the blood or spinal fluid. Clinical results were as follows: Markedly improved, 32.6 per cent; improved but unfit for visit home, 15.8 per cent; unimproved, 31.6 per cent; aggravated, 0.9 per cent; relapsed, 2.9 per cent; died directly or indirectly from malaria, 7.9 per cent; died from other causes, 7.9 per cent. He believes that the therapy should be administered in every case in which the physical condition does not contraindicate its administration.

Schizophrenia and Psychotherapy.—BRILL (*Am. J. Psychiat.*, 1929, 9, 519) believes that only those acute schizophrenics who cannot be kept at home should be sent to sanitariums and they should only stay there until the acute process subsides. He calls attention to the hopeless prognosis formerly held in reference to schizophrenia and Professor Freud's early suggestions that cases of dementia precox should not be psychoanalyzed. He presents a group of cases which made excellent adjustment when treated without hospitalization and were successfully carried through to a conclusion of their illness with good insight and good adjustment. He believes that since the essence of the schizophrenic psychosis is a withdrawal from the world of reality that hospitalization in cases where it is not absolutely necessary tends to favor the withdrawal and to fix the individual into an institutionalized adjustment from which it is very difficult to release him. "As disagreeable as this may sound to you, it is none the less true that practically all the hospitals and sanitariums for mental diseases seem to be especially arranged to bring about this very sad result." In those cases where hospitalization is necessary the patient should be discharged from the hospital as soon as possible, but all of these patients must be followed over a very long period of time in order to prevent recurrences of the condition and to insure a continuation of the adjustment reached.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Sensitization to Saprophytic Fungi.—Comparatively little has been written on the sensitization of human beings by the spores of common saprophytic fungi. The spores of a great variety of these fungi are practically universally distributed in the air. A patient with asthma and eczema, studied by HOPKINS, KESTEN and BENHAM (*Proc. Soc.*

Exper. Biol. and Med., 1930, 27, 342) was found to be sensitive to a species of *Altenaria* by skin and inhalation tests, as well as to a common saprophyte *Aspergillus nidulans* isolated from an eczematous lesion of the leg, and to other fungi obtained from house dust. The authors had some difficulty in interpreting certain of their results because of the known sensibility of eczematous skin to nonspecific irritation.

Intestinal Bacterial Flora and Microbic Permeability in Relation to Nutritional and Meteorologic Changes.—Disturbances in the equilibrium between parasites and the host must be more fully recognized if we are to understand the importance of the varying factors in certain diseases. ARNOLD (*J. Hygiene*, 1929, 29, 82) has studied among such factors, the influence of sudden changes in the acid-base equilibrium in inhibiting the destruction of bacteria by the intestinal mucosa, and in permitting the penetration of bacteria into the thoracic duct. Climatic changes have been shown to affect the susceptibility to infection, and nutritional factors must be considered as inseparable from those of climate. The beneficial effect of a changing nutritional and meteorologic environment on the tonus of the physiologic systems is emphasized, but it is also indicated that these alternations in environment must not exceed the power of the organism to adapt itself to these changes. The bearing of these principles on the incidence of seasonal outbreaks of various intestinal diseases is discussed and much experimental evidence is presented in demonstration of his thesis.

Immunization of Chickens Against Fowlpox.—A variety of methods have been used in the preparation of materials for vaccination against fowlpox. KLIGLER (*Brit. J. Exper. Path.*, 1930, 11, 10) treated the infectious materials obtained from the skin lesions by heat, formalin and phenol. The crusts from the skin contain active virus in large quantities, and lend themselves for the production of a vaccine. The author found that fowlpox virus heated to 56° C. for one hour, or treated with 0.5 per cent formalin solution for four days no longer infects susceptible chickens, and fails to produce immunity. Phenolized vaccine (0.25 per cent) contains active virus from three to seven weeks after preparation and though this will no longer induce active lesions, it will produce immunity. The failure of heated phenolized vaccine to produce immunity while the same material unheated will protect, indicates that the immunity was induced by a living virus.

Mixed Tumors of the Palate.—The term mixed tumor is applied to histologic complex neoplasm in which a variety of tissue elements constitute a part of the progressive growth. These tumors arise, not uncommonly, about the face and mouth, being most frequently observed in the parotid gland. D'AUNOY (*Am. J. Path.*, 1930, 6, 137) reports two cases of mixed tumor of the palate in women aged twenty-five and forty-three years respectively. The tumors were similar in type both being encapsulated masses, made up of glandular tissue embedded in a myxomatous cartilaginous stroma. Attempts at epithelial keratinization were observed in one of them. These tumors, in this location, are not common, there being less than one hundred in the literature. For

the most part, mixed tumors possess only a local malignancy, and will recur if not completely removed. There is no agreement, up to the present time, as to the origin of the individual elements composing the mixed tumor. The author leans to the theory of embryonal enclavement.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Postvaccinal Encephalitis.—ARMSTRONG (*Pub. Health Rep.*, 1929, 44, 2041) notes that nervous manifestations have long been known to follow such acute infections as smallpox, chickenpox, measles, mumps, etc. Postvaccinal encephalitis belongs to this group. The history of the complication is reviewed, several hundred cases having occurred in Europe. The onset is usually sudden and occurs from the tenth to the thirteenth day after vaccination—that is, when the vaccination is at its height. The symptoms are fever (104° F. or more) vomiting, headache and stupor or coma. Death occurs in from 30 to 40 per cent of cases. Recovery, when it occurs, is rapid and complete, save in a few cases where crippling results. The cause of the complication is unknown; animal tests have been negative. Several cases have occurred in the United States and it is suggested that reports of cases observed be made to the U. S. Public Health Service.

Leprosy.—During a clinical study of leper patients in Hawaii, WAYSON and BADGER (*Pub. Health Rep.*, 1929, 44, 2871) obtained findings suggestive of disturbances of carbohydrate metabolism with remarkable frequency. About 23.4 per cent of the cases showed glycosuria and the percentage of positives was markedly increased by feeding glucose. It was also found that the average basal blood-sugar percentage was higher than normal. The excess of sugar in the urine was larger among female patients. The tests were controlled by the examination of blood and urine of nonlepers. The writers regard these findings as indicative of a high incidence of carbohydrate metabolism among lepers. They point out that leprosy affects chiefly the skin and nerve tissues and that in diabetes these tissues are also often involved. WAYSON (*Ibid.*, 3095) has analyzed the results of the treatment of lepers in Hawaii over a period of many years. Medical treatment, chiefly with respect to chaulmoogra oil and its derivatives, is described and reference is made to symptomatic and hygienic measures.

With respect to the latter, an attempt is made to place all patients under hygienic and sanitary conditions which will contribute to their general health and favor the marshaling of their resistive and reparative forces. Definite conclusions concerning the efficacy of these methods in hastening or accomplishing recovery from leprosy cannot be drawn at this time, but their apparent efficacy in the treatment of analogous diseases, and the results thus far obtained in leprosy seem sufficient to warrant their expansion and more intensive application while investigations are continued toward the development of more definitely remedial measures or agents. The number of annual admissions and the probable rate of incidence of leprosy in Hawaii are both falling, and it appears that biologic and other agencies may be causative factors in the decline, and that the effect of the mandatory segregation of cases for the past sixty years is indefinite. However, the measure seems to be economically feasible, and is justifiable and desirable in the community, because of its potential value in controlling the dissemination of the disease, and because of its value in facilitating the treatment of the individual patient and the investigation of the pathogenesis and treatment of the disease in general. The use of chaulmoogra oil and its derivatives in Hawaii for ten years has not been attended by results which indicate that they have any specific therapeutic value, and any effect they may have remains undetermined. Symptomatic and hygienic treatments under hospital or sanitarium régime probably aid in the recovery of some patients; but further properly controlled observations over several years are needed to determine this. Studies of pathogenesis, early diagnosis, and treatment with the facilities offered to modern medical research are required for the promotion of more effective results than are being obtained. DENNEY (*Ibid.*, 3169), who studied leprosy in the National Leper Home at Carville, La., remarks on the hopeful outlook in the treatment of the disease in a considerable number of patients. During the fiscal year 1928-1929, among a leper population of about 300, 19 were released as arrested cases and no longer a menace to the public health. Six additional cases might have been placed in the same class but were retained in the hospital for humanitarian reasons. About half the patients take chaulmoogra oil by mouth and about the same number take it by hypodermic injection. A few take the ethyl ester preparations. The various services furnished by the hospital are described briefly. About a third of the patients give a positive serologic test for syphilis. Tests were made on the sputum of 210 lepers and of these 99 showed acid-fast organisms. Seventy-five of these were tested by guinea-pig inoculation and 14 were positive for tuberculosis.

Vaccinia: Studies of Immunity, Reactions and Effects of Heat.—ANDERVONT and ROSENAU (*J. Immunol.*, 1930, 18, 51) obtained a reaction following the introduction of heated vaccine virus into the skin of previously vaccinated persons. This was noted during the course of experiments in which heated material served as "control" for unheated virus. These experiments confirm the findings of others and also indicate that with the single scratch method of vaccination, virus heated to 70° C. for one hour, kept in boiling water for one hour, autoclaved for one hour or kept at room temperature for five years is capable of eliciting the response in previously vaccinated individuals; in fact, the

reaction following the use of heated virus was as constant as that observed when unheated virus was employed. The reaction to heated virus appears and disappears somewhat earlier than the reaction to unheated virus. The heated virus produces a reaction with papules indistinguishable from the well-known immediate reaction. It was also found that no reaction occurs when heated virus is used to vaccinate previously unvaccinated children or adults, and that such vaccination induces no immunity. The writers' studies concerning the antigenic substance responsible for the immediate reaction tend to show that the virus is the causative factor. An extract of vaccine pulp freed of virus by filtration is incapable of causing the reaction. Furthermore, individuals immunized against cowpox by vaccination with calf virus give the immediate reaction when revaccinated with vaccine virus derived from rabbit brain. These results indicate a common antigen in calf and rabbit material. The vaccine virus is known to be present in both. The possibility of another antigenic substance being responsible is excluded because normal calf skin or glycerinated normal rabbit brain fail to evoke any reaction in previously vaccinated persons.

The Epidemiology of Diphtheria and Scarlet Fever in the Subtropics with Special Reference to the Syrian States Under French Mandate.—PARR, GOODALE and KIRSCHNER (*J. Prev. Med.*, 1930, 4, 39) performed Dick tests on 714 and Schick tests on 878 persons living in the Syrian States under French mandate and found that the people of this area possess a remarkably high resistance to the toxins of diphtheria and scarlet fever. A study of government reports of morbidity and mortality and a medical census of 2301 persons show that clinical cases of scarlet fever are very rare and that diphtheria is only slightly more common. It is suggested that subclinical diphtheria is common and that it is probably the cause of the diphtheria immunity. As regards scarlet fever there is less evidence that subclinical immunization is responsible for the existing immunity. In view of prevalent streptococcal infections of the throat and middle ear and the low puerperal sepsis rate, it is possible that immunity against puerperal sepsis and scarlet fever is built up at an early age by infections with the streptococcus in other and milder clinical forms. Measles is common in the area in question. This lends support to the view that the etiologic agent of this disease has no very close relationship to that of scarlet fever. Further, for tropical and subtropical countries at least, measles may be thought of as a younger disease than either diphtheria or scarlet fever.

Current Studies of Undulant Fever.—HASSELTINE (*Pub. Health Rep.*, 1929, 44, 1659) discusses the present status of undulant fever in the United States. The disease was reported in this country first twenty-four years ago when Craig reported a case and prophesied that it would be found to account for some of the " . . . obscure continued fevers which are prevalent. . . ." The disease is now being recognized quite frequently. The prevalence seems to vary greatly in different parts of the country. The diseases likely to be confused with undulant fever are tuberculosis, typhoid and paratyphoid fevers, rheumatism, malaria, influenza, focal infections, tularemia, and a few others. The chief symptoms are weakness, headache, or general aching, fever, chilli-

ness or chill and profuse sweating. The sweating is often confined to the upper half of the body. The temperature may be normal in the morning and go to 104°F. in the afternoon. Characteristic febrile waves may occur separated by afebrile periods. Some cases have only one wave; others have recurrences during one to three years. Diagnosis is aided by positive agglutination titer in the serum and made positive by a successful blood culture. The infection seems to originate most often with cows, less frequently swine and rarely goats. Persons may acquire the disease from handling infected animals, or animal products, or by the use of milk from such animals. The ideal prevention would be the elimination of the disease from animals, and this is believed to be a possibility. Pasteurization, or boiling, of milk would prevent milk-borne cases.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 19, 1930

Hair Groupings in the Skin of the Albino Rat.—D. A. FRASER (from the Department of Anatomy, University of Pennsylvania). The arrangement of hairs into groups was studied on the dorsum and on the venter in microscopic sections cut at right angles to the length of the hair follicles. Groups may be considered in two classes, for example, those with and those without a central follicle, which must contain a hair twice the diameter of the other hairs in the group. Follicles can be classified according to their location within a group, as central, containing a central hair; adjacent, the remaining follicles within such a group; and associate, those in groups without a central follicle. Follicles may be single, or composite, that is, containing more than one hair. The hairs in groups with a central follicle average 13.9 on the dorsum and 17.2 on the venter, distributed in 6.05 and 7.4 follicles, respectively. Hairs in groups without a central follicle average 8.7 on the dorsum and 9.7 on the venter, distributed in 3.8 follicles in both cases. During the winter months there are 7.7 groups, 35.75 follicles and 85.65 hairs to an average square millimeter of dorsal skin and 11.5 groups, 54.7 follicles and 152.60 hairs to an average square millimeter on ventral skin. It is estimated that the body hairs number 5,028,303 in the male albino rat of 230 gm. of body weight. It is hoped that these counts can be used as a standard for those experimentalists who report the hair as being more luxurious or more sparse as a result of dietary or endocrine conditions.

Comparison of the Hydrogen and the Glass Electrode in the Determination of the pH of Serum.—W. C. STADIE and H. O'BRIEN (from the Department of Research Medicine, University of Pennsylvania). A simple glass electrode was constructed which can be maintained at 38°C. and by which the pH of serum or whole blood may be deter-

mined with a high degree of accuracy. One to 2 cc. of serum is required which is collected by a technique which prevents loss of carbon dioxide and transferred to the electrode from a syringe or mercury receivers. Equilibrium is reached in two to four minutes, and E.M.F. of the glass cell is read to within ± 0.1 mV. by means of a stable and sensitive electron tube potentiometer. Various controls were done to show the reliability of the method. A series of sera were compared as to their pH by the hydrogen electrode and the glass electrode and a close agreement found which averaged about ± 0.007 pH units.

The Structural Composition of the "Bone Solid."—S. E. POND (from the Laboratory of Physiology, University of Pennsylvania). Two series of experiments are reported which are part of a study of the inorganic composition of bone and homologous tissues. They were planned to add to information concerning the bone phosphate. Previously it had been shown that the ratio:

$$\frac{\text{Total inorganic P}_2\text{O}_5}{\text{Total CaO, less CaO equivalent to CO}_2}$$

had yielded values indicating the calcium phosphate in bone to be more basic than tricalcium phosphate. It was not known whether the ratio as calculated was a true index of the phosphate component and particularly the calcium phosphate, since the combination of calcium with protein and with carbonate had not been measured.

The material studied was bone which had been prepared from whole skeletons of rats and rabbits grouped as to age. The marrow lipoids were removed by hot alcohol. Drying was done over sulphuric acid. Analyses of the bone powder were made by several methods found to yield satisfactory results in the study of the inorganic materials concerned. The data represent ash, total CO_2 , CaO, P_2O_5 and MgO, with respect to age. This dried powder was used to determine: (a) the calcium bound by protein and (b) differences in solubility of material as a guide to the molecular structure of calcium phosphate in bone.

A. Samples of powdered bone were treated with 0.5 N HCl in small portions and leached with 0.001 N HCl until calcium-free. This powder was adjusted to pH 3 in dilute acid and found to retain no calcium from calcium chloride solution. Samples of the same powder were ashed and found free of calcium. Portions were adjusted to pH 5.5 and found to retain calcium. The amount of calcium bound by the powder at pH 5.5 was measured by removing in acid solutions and analyzing as oxalate. The amount was different for bone from adult and from newborn skeletons, viz.: 0.95 mM Ca per gram dry isoelectric powder and 0.7 mM Ca per gram dry powder, respectively. Deaminized powder from adult skeletons was found to combine with 0.92 mM Ca per gram dry isoelectric powder. The results indicate a combination with some ampholyte and apparently with carboxyl groups. The amounts are significant, and indicate some differences in combining power with respect to age. The experiments are being continued with standardized laboratory animals of known age representing four species.

B. Several attempts to secure calcium-free powdered bone for the above study had demonstrated a marked difference between the

inorganic components of the bone from adults and from very young animals when used in acid solutions. Powdered bone from whole skeletons of newborn animals (rat and rabbit) was made calcium-free in dilute acid solutions and in salt solutions between pH 3 and pH 4. Bone from adults required stronger acid solutions, such as 0.5 N HCl, to dissolve the calcium phosphate. Powdered bone from adults when treated and leached on filters could only with difficulty and with excessive amounts of reagent be freed of calcium when 0.05 N acid solutions were employed as solvents. The same material when so treated or shaken for long periods, but with 0.005 N HCl and with HCl:Na acetate adjusted to pH 2.03, retained over 80 per cent of the total calcium.

A graded series of solutions with respect to pH was employed to indicate differences in the calcium phosphate. This consisted of HCl = 0.5 N, 0.1 N, HCl:KCl pH 0.94 and pH 1.87 and HCl:Na acetate 1.09, 2.03, 4.19 and 6.31.

1. Bone from newborn animals: all of Ca, Mg, P and CO_2 dissolved in pH 4.19. Shaken sixteen hours at 25° C.; solutions changed after two, four and eight hours.

2. Bone from adults: all of Mg and CO_2 dissolved in pH 4.19, but only 15 per cent of total P and 20 per cent total Ca. Shaken sixty-four hours, as above, except solution changed after sixteen hours.

Complete solution in pH 1 HCl, in pH 0.94 HCl:KCl and pH 1.09 HCl:Na acetate but not in pH 1.87 HCl:KCl nor HCl:Na acetate pH 2.03 within limits of experiment.

It is concluded that the bone phosphate has a different composition with advancing age and is no more basic than $\text{Ca}_3(\text{PO}_4)_2$ in the bone of embryos and newborn animals examined. Some more basic phosphate is present in bone of older animals. The structure of this material is being studied further with chemical and physical criteria.

Experimental Study of the Van den Bergh Reaction.—J. G. REINHOLD and H. F. SNIDER (from the Biochemical Laboratory of the Philadelphia General Hospital). A close relationship exists between the concentration of bilirubin in serum, estimated as icterus index, and the type of direct van den Bergh reaction. Immediate reactions were associated with high bilirubin values and delayed reactions with low values. Between these extremes biphasic reactions were most frequently observed. Working on the hypothesis that speed of color formation after the addition of diazo reagent might be governed by variations in the concentration of bilirubin in the serums, the behavior of solutions of pure bilirubin in human serum was studied. A series of such solutions containing approximately the quantity of bilirubin found in the serum in jaundice showed progressively negative, delayed, biphasic and immediate reactions as the concentration increased. Pathologic serum of the immediate reaction type diluted with normal human serum also was converted to the biphasic, delayed, or negative reaction type, depending on the degree of dilution. Delayed reactions became biphasic when the temperature of the reacting materials was increased from 15° to 30° C. Other factors, such as hydrogen-ion concentration, capable of changing the type of reaction, ordinarily do not vary enough to influence appreciably the interpretation of the test.

Therefore, the results given by the direct van den Bergh reaction depend upon the concentration of bilirubin in the serum and not upon changes in the molecular or physical state of the bilirubin.

The Action Potential Wave in Nerve During and After Oxygen Lack.—W. R. AMBERSON, A. PARPART and G. SANDERS (from the Laboratory of Physiology, University of Pennsylvania). The low-voltage components of the single action potential wave¹ have been followed in frog nerve, during and after a period of oxygen lack. The "after positivity" quickly disappears in pure nitrogen. The negative retention is at first exaggerated and then suppressed, long before the disappearance of the high-voltage phase of the wave. Upon the readmission of air the negative retention reappears again within a few minutes and becomes very highly developed, producing a rise in maximal deflection of the galvanometer to values much exceeding those previously obtained in air or in nitrogen. An "after positivity" also reappears.

By a direct method of analysis it has been found possible to follow the time relations of both high- and low-voltage phases of the action potential wave. The initial high-voltage phase undergoes no such changes as are seen in the low-voltage elements which succeed it. In nitrogen the high-voltage phase continues for several hours unchanged, then slowly is reduced to nothing; upon the readmission of air it quickly recovers its original value. No postasphyxial overshoot is seen. It is concluded that the two elements of the action potential wave are the electrical signs of two separate processes, one of which, associated with the high-voltage phase, is relatively anaërobic, while the other, presumably a recovery mechanism, connected with the persistent low-voltage elements, is relatively aërobic in nature. At least it may be stated that the retentions are much more sensitively related to the presence or absence of oxygen than is the high-voltage phase.

¹ Amberson and Downing: J. Physiol., 1929, 68, 19.

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SPECIAL MINUTE CONCERNING THE DEATH OF DR. PAUL A. LEWIS

AUTHORIZED AT THE SESSION OF OCTOBER 21, 1929

IN November, 1928, Dr. Paul A. Lewis offered his services to the Rockefeller Foundation for the accomplishment of a project to extend the study of yellow fever in South America, earlier made by his friend Noguchi. His offer was accepted; and from January 15 to June 25, 1929, he worked in the laboratories of the International Health Commission in Bahia, Brazil, on the nature of the virus of yellow fever. On the latter date, he was stricken with that disease and died on June 30, 1929.

Paul Adin Lewis was born in Chicago, Illinois, on April 14, 1879. His father was a physician, and as a boy he used to drive the horse on his father's professional visits. From this association a passion grew in him to become a "good doctor." His medical training was obtained in the University of Pennsylvania, where he graduated in 1904. Here, under the inspiration of Flexner, he developed an interest in research in pathology and he soon came to feel that his ambition to be of service to medicine could best be accomplished in a career of investigation. After graduation he served as interne in pathology in the Boston City Hospital under Dr. Frank B. Mallory. The following three years, 1905-1908, he came under the influence of Professor Theobald Smith in the Massachusetts State Laboratory of Health and for two of these years held the Austin teaching fellowship in pathology in the Harvard Medical School.

The years 1908-1910 were spent in work at the Rockefeller Institute in New York in direct association with Simon Flexner. In 1910 he came to Philadelphia as director of laboratories of the Henry Phipps Institute of the University of Pennsylvania, a position he held until 1923. During all of this time he was also a member of the Medical Faculty of the University, first with the title of Assistant Professor of Pathology (1910-1921), later as Professor of Experimental Pathology (1921-1923). He also served as director of the Ayer Clinical Laboratory of the Pennsylvania Hospital from 1911 to 1916. In 1923 he resigned from his positions in Philadelphia to become associate member of the Rockefeller Institute, electing to serve with Theobald Smith in the Institute of Animal Pathology at Princeton. From Princeton he went to Brazil.

Thus for almost exactly twenty-five years he devoted his best energies to investigations in pathology. The results of his work were conspicuous and secured for him both a national and international reputation as one of our most competent pathologists. He and Auer were the first to discover the mechanism of anaphylactic death in guinea-pigs. His work with Flexner on poliomyelitis and on the nature of poliomyelitis virus is classical and his part in this was more than that of subordinate assistant.

During the first years of his directorship of the Phipps Institute he organized a staff for the comprehensive study of the chemotherapy of tuberculosis, believing with firm conviction that a specific agent against this disease is to be found. His hope was not realized, but the results of his study of hundreds of compounds may serve as a sound foundation for future work in this field.

In collaboration with Sewall Wright of Washington, using guinea-pigs whose heredity was known for many generations, he made masterly beginnings of a descriptive and analytical study of heredity factors in susceptibility and resistance to tuberculosis, discovering the fact that the inheritance of resistance is a dominant trait in the Mendelian sense. He discovered and described as "allergic irritability" the heightened capacity of the animal body, infected with tubercle bacilli, to react to nonspecific substances with increased production of antibodies.

His early developed interest in filterable virus was continued in his Princeton period in studies on hog cholera and on hog influenza, the latter giving promise in his opinion of important developments in relation to pneumonia in man. This interest was an important factor in his decision to volunteer to study the yellow-fever problem.

We are as yet ignorant of the permanent value of his studies of yellow fever. He himself did not rate them very highly. He went to South America knowing that it would be extremely difficult to add materially to the work of Noguchi, but he was impelled to undertake the task chiefly because of loyalty to a close friendship of twenty years.

During the World War, Dr. Lewis searched for ways of making his capabilities valuable to the medical services of our forces. Very soon after our entrance into the war he organized a group of four workers, of which he was one, to aid the Surgeon-General of the Army in discriminating among the various means, urged upon him, for combating infections. Later in the summer of 1917 he volunteered for service in the Navy, was commissioned Assistant Surgeon with the rank of Lieutenant (Junior grade), and with the permission of the University authorities placed the laboratory of the Phipps Institute at the disposal of the government. The laboratory became the central station in this district for the production of typhoid vaccine, and from it he directed bacteriologic surveys for the detection of meningococcus carriers among the Navy personnel. His services were recognized by successive promotions to the grade of Medical Inspector with the rank of Commander.

The most conspicuous qualities of his character were courage, loyalty and unselfishness. The force which these qualities gave to his investigative insight and zeal made him one of the most influential factors in the development of medical science in Philadelphia during his years here. His courage was exhibited in the difficulty and magnitude of the problems which he chose for study; in the plans which he made and fought for in the institutions with which he was connected; in his decision to abandon his influential directorship of the laboratories of the Phipps Institute in order that his own scientific efforts should not be impeded by administrative duties; and finally by his decision to volunteer in the yellow-fever work.

His loyalty to his profession, to the community, and to the University was demonstrated repeatedly in the plans which he constantly advocated for greater utilization and extension of the methods of research in their medical problems. He was a leader in almost every one of the organizations in Philadelphia devoted to medical research,

among them the Physiological Society of Philadelphia. Evidence of his unselfishness is to be found not only in the record of his deeds but in the affection in which he was held by those who were associated with him in his work. Not only was he a wise counsellor but in numberless instances he was the author of plans by which the work of his colleagues could be made happier or more productive.

The preparation of this statement is dictated by the desire of the members of this Society that its permanent records shall contain an expression of their sense of loss because of the death of a loved colleague, and by the hope that they may reveal the basis for feelings of pride cherished by the members in his spirit, his accomplishments and the circumstances of his death.

The Roll of Honor of this Society now holds two names:

ALFRED REGINALD ALLEN

who was killed on the field of battle in France in 1918

and

PAUL ADIN LEWIS

who died as a volunteer in the fight against yellow fever.

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ORIGINAL ARTICLES.

STUDIES ON THE CIRCULATION OF THE FEET IN DIABETES
MELLITUS WITH AND WITHOUT GANGRENE.

BY ISAAC STARR, JR., B.S., M.D.,

ASSISTANT PROFESSOR OF CLINICAL PHARMACOLOGY; ASSOCIATE IN MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

(From the Medical Division of the Hospital of the University of Pennsylvania).

THE purpose of this investigation was to discover whether aid in the diagnosis and prognosis of peripheral vascular disease could be secured by a study of the circulation in the extremities by certain physiologic methods. The observations recorded hereafter do not afford a solution of the problem attacked but represent an attempt to develop the means whereby a solution may be attained in due time.

In order to obtain data on pregangrenous conditions a large number of patients suffering from a disease frequently complicated by gangrene (diabetes mellitus) have been examined and it is hoped that they can be followed for many years, and the incidence of gangrene determined. In the meanwhile it has been found that the response of the skin to histamin together with the physical findings permits an analysis of the conditions of the circulation in the extremities which cannot be obtained by physical examination alone. This communication seeks to present the methods employed in this analysis, to record the findings in many diabetics who do not have trouble with their feet and in a small number with gangrene, and to point out the significance of these findings as judged from the incidence of trouble already present.

As gangrene of the feet in diabetes has been generally attributed

to a decreased blood supply due to arteriosclerosis the investigation commenced with determinations of "bloodflow" through the feet by the calorimeter method of G. N. Stewart.¹ While interesting results were obtained, this method proved too time consuming to permit the accumulation of enough data to provide the desired information.

The observation of Sir Thomas Lewis² that the experimental interruption of the circulation to an extremity prevented the normal development of the skin reaction to histamin, and his conception that this reaction is purposive, producing the local changes required to defend the cells from injury, suggested that the reaction of the skin to histamin might be used as a means of roughly estimating the state of the circulation and the resistance to infection of the extremities.³ This method has proved simple and rapid enough for routine clinical use. Therefore the normal variability of the reaction, the variation caused by change of temperature, by change of position and by administration of certain drugs have been determined. The reaction has been elicited in a control series of over 100 cases which includes normal persons and patients suffering from cardiac disease, arteriosclerosis, hypertension and from many disease conditions never complicated by gangrene of the extremities. Finally, over 100 diabetics have been tested.

The results show that over one-half the diabetics tested have diminished circulatory responses on their feet which persist despite control of the metabolic defects by diet and insulin; in 34 per cent this impairment is marked. Into this latter group fall the great majority of cases with gangrene and with evidence of circulatory impairment.

The response of the skin to histamin together with the physical findings permits the clinical demonstration of conditions of the circulation not easily recognized by other means, namely: the presence or absence of compensation for sclerosis of large arteries, and the presence of abnormal reactions in small vessels without noteworthy involvement of larger arteries. By means of such information the diabetics may be divided into groups according to the type of circulatory disorder; in two of these the incidence of trouble with the feet was 54 per cent and 36 per cent; in the remainder such trouble was almost completely absent. This high incidence in certain groups plainly suggests that patients showing certain types of reaction and certain physical signs have a much larger chance of developing gangrene than the others; a reexamination of the series at a future date should provide decisive information.

Estimations of the Circulation of the Feet by Stewart's Calorimeter Method. The calorimeter was constructed, the determinations performed, and the results calculated according to Stewart's directions.¹ Most of the estimations were made with the patient in the sitting position. The feet after fifteen minutes immersion in a bath

TABLE I.—A COMPARISON OF THE CLINICAL EXAMINATION OF THE FEET WITH THE CALORIC OUTPUT.

Subject.	Age.	Diagnosis.	Blood pressure mm. Hg.	Caloric output of feet (cal. per min. per 100 cc.).		Bloodflow of feet according to Stewart (gm. per min. per 100 cc.).		Clinical examination.
				Right.	Left.	Right.	Left.	
S A. Wi	30 26 65	Normal Duodenal ulcer Diabetes. Auricular fibrillation	125/72 120/72 140/60	19.4 18.7 16.0	4.4 (2)* 3.9 (1) 3.6 (1)	Negative. Negative. Heart enlarged, absolutely irregular, arteries moderately sclerotic, feet negative, dorsalis pedis pulses palpable.
M. L. J. W.	13 43	Diabetes Diabetes	120/70 110/64	13.4	16.2 13.9	2.6 (1)	3.0 (1) 2.3 (1)	Heart, vessels and feet negative. Heart negative, vessels somewhat thickened. Feet negative except for absent dorsalis pedis pulsation.
J. M.	45	Hemochromatosis	110/68	8.9	1.9 (1)	Very weak, heart and vessels negative, feet negative except for slate-colored skin.
C. H. S.	32	Diabetes	8.8	1.3 (1)	Heart and vessels negative. Dorsalis pedis pulse just palpable, feet otherwise normal.
M. B.	37	Diabetes	115/75	5.6	1.2 (1)	Heart, vessels and feet negative. Dorsalis pedis pulse strong.
Mae N. J. S.	26 19	Diabetes Diabetes	100/60 122/76	9.4 6.0	7.4 5.5	1.2 (2) 0.9 (4)	0.7 (2) 1.1 (2)	Heart, vessels and feet negative. Recovering from acidosis. Heart and vessels negative, feet always cold to touch, otherwise negative, dorsalis pedis pulse strong.
J. H.	42	Diabetes	80/50	4.7	4.2	0.7 (7)	0.6 (7)	Recovering from acidosis. Heart negative, moderate sclerosis of arteries, edema of feet on prolonged standing, none when tested. On allowing feet to hang down they acquired a purplish tinge, the color returning in four seconds after being obliterated by pressure. Dorsalis pedis easily palpable. Feet always cold to touch.
S. G.	35	Gastric ulcer	85/50	3.1	3.6	0.6 (3)	0.9 (3)	Heart and vessels negative, feet become dusky purple when held down, color returns in 15 to 20 seconds after being obliterated by pressure. Right dorsalis pedis pulse easily palpable; left doubtful. Feet cold.

* Number in parenthesis indicates number of determinations made, each on a separate day. In the cases in which more than one determination was made the average caloric output and bloodflow figures have been given.

at about 32° C. were placed in the calorimeter filled with water at the same temperature, the rise of temperature of the water being measured. The foot was then withdrawn, and the loss of heat from the calorimeter to its surroundings determined.

Criticisms of this method have appeared which indicate that the figure for bloodflow given is too small. Harris and Marvin⁴ have demonstrated that the temperature of the blood in the hand veins does not fall to that of the water in which the hand is immersed; this is doubtless true of the feet also. Stewart⁵ realized this possibility and regarded his method as giving a figure below which the bloodflow could not lie. Therefore the results recorded in Table I have been expressed both as calories given off and as "bloodflow." Since the body temperatures were all within the normal range and the bath temperatures varied only between 30.2° and 31.7° C., the calories given off are to be regarded as a function of the bloodflow. The inclusion of Stewart's "bloodflow" figure permits comparison with other determinations by this method. The relative agreement between the two sets of figures is obvious.

In this investigation the method has been used only to compare the bloodflow through the feet of normals with that of diabetics and to compare the flow in the same patient, before and after control of his metabolic defect. The similarities and the large differences found are significant. The errors in the method pointed out by Sheard⁶ are too small to be of significance in this investigation.

Repeated determinations on four normal subjects made by Stewart⁷ under conditions similar to our experiments showed results ranging from 2.86 to 7.91 cc. of "bloodflow" per minute per 100 cc. of foot. My determinations on three normal subjects yielded figures of 4.5, 4.4 and 3.9 cc. per minute per 100 cc. of foot.

The patients tested were all in the wards of the University Hospital. Table I summarizes the results obtained, certain data on 3 diabetics and 2 normals mentioned previously³ have been included in it. Table II gives the results of repeated determinations on 2 diabetics. It is obvious that the majority of the diabetics tested have a calorie output from their feet far under that of normal persons. Discussion of other significant findings will be reserved until the results of the histamin test have been presented.

Estimations of the Circulation of the Feet by the Histamin Reaction. The physiology of the skin reaction to histamin has been elucidated by Sir Thomas Lewis.⁸ The technique of eliciting it has been described.³ The only change has been the addition of 0.5 per cent of chlorotone to the 1 to 1000 solutions of histamin acid phosphate (also called ergamin acid phosphate). This acts as a preservative. After keeping such a solution at room temperature for three months the reaction of the skin to it could not be distinguished from that to a fresh solution containing no chlorotone.

TABLE II.—CALORIMETRIC DETERMINATIONS ON PATIENTS SUFFERING FROM ACIDOSIS AND AFTER RECOVERY FROM IT.

Patient.	Date, 1925.	Circulation in feet (gm. per min. per 100 cc. of foot).		Urine.		Fasting blood sugar mg. per 100 cc.	Diet P. F. C. gms. per day.	Units of insulin before				Remarks.
		Right.	Left.	Sugar gm. per day.	Diabetic acid.			Break- fast.	Lunch.	Supper.	Mid- night.	
J. H. Age 42	April 17	0.5	0.7	51.8	++	330	45-50-31	30	0	10	0	Foot sore. Soreness gone.
	April 20	0.5	0.3	26.8	++	60-155-76	35	0	15	0	
	April 24	2.0	1.5	2.7	++	395	61-155-75	35	0	15	10	
	April 28	0.3	0.5	0	0	104	56-150-60	30	0	10	10	
	May 2	0.6	0.3	0	0	57-149-61	20	0	5	10	
	May 7	0.5	0.2	0	0	173	88-150-63	30	0	10	10	
	April 5	0.4	+	++	223	46-67-56	0	30	10	10	
	April 6	0.4	0.4	23.9	++	271	52-108-59	30	0	10	10	
J. S. Age 19	April 7	0.3	1.9	+	++	51-78-61	30	0	10	10	Left hospital.
	April 8	2.4	+	0	62-97-50	30	0	10	10	

The patients were placed flat on their backs with legs extended. Areas of normal skin were cleansed with alcohol and after complete evaporation a drop of the histamin solution was placed on the surface. With a sharp needle the skin was pricked seven times through the drop, the pricks forming a circle about 5 mm. in diameter, the needle going well into the skin but not deep enough to draw blood. Usually one test was placed above the knee, one about 6 inches below the patella, a third 6 inches above the ankle, a fourth on the dorsum of the foot; in special cases other situations were tested. The resulting reactions were roughly sketched at two and a half, five, ten, and fifteen minutes after initiating them. The reactions normally resulting resemble mosquito bites: first a red spot appears, followed and obliterated by a wheal, surrounded by a reddened area (flare) several centimeters in diameter; a sensation of itching accompanies the reaction.

The series of reactions on normal persons and patients with normal circulations³ has been extended to include over one hundred determinations.

The normal reaction is complete (that is, both wheal and flare present) within five minutes and the reactions on the foot closely resemble those on the leg and thigh, the distal usually appearing a little slower and being a little less well formed than the proximal. Evidence of diminished circulation in the feet consists of delay in appearance and imperfect development of the reaction on the foot, while the reaction above the knee remains normal.

The results recorded hereafter have been classified solely according to the time of appearance of the wheal and flare; that for the wheal being the time at which it could first be palpated. Useful information can be obtained by observing the height and sharpness of margin of the wheal and the intensity of color of the flare and by comparing different reactions along the leg. But as a rule these features vary inversely with the appearance time, so no attempt has been made to record them separately. As the reactions on the legs usually occupied an intermediate position the discussion will be confined to those on the feet and above the knees. For convenience of expression, the normal reaction, complete within five minutes on both foot and knee, will be spoken of as Grade I; a reaction on the foot lacking wheal or flare or both at five minutes but complete within ten minutes, the reaction above the knee being normal, will be referred to as Grade II; a reaction on the foot failing to become complete within ten minutes, that above the knee being normal, will be called Grade III.

Control Observations on Nondiabetic Subjects. Before proceeding to a discussion of the findings in diabetics it is desirable that several physiologic and pathologic factors which modify the velocity of the histamin reactions be considered. Some of these indicate conditions which must be controlled when the test is made, others enter into the interpretation of the results on certain patients.

The Variation in Speed of Whealing Inherent in the Method, and that Caused by Change of Temperature and of Position, by Drugs, and Skin Abnormalities. The appearance of the wheal can be more accurately timed than other parts of the histamin reaction. The variation in velocity of whealing inherent in the technique of eliciting the reaction varies with the condition of the circulation. Thus whealing on the normal forearm takes place in about two minutes and duplicate wheals usually appear within fifteen seconds of each other. On the normal foot, where wheals appear in about three minutes, duplicate reactions may be expected to appear within one minute of each other. On abnormal legs which wheal in about twelve minutes as much as three minutes may separate duplicate determinations.

Variations in ward temperature have made no significant difference in the velocity of whealing. Cooling the feet by sponging with alcohol and allowing evaporation caused a delay of about one minute in 2 cases. Extremes of cold cause profound alteration in the reaction.⁹ When the feet are cold delayed reactions should not be accepted as indicating pathological diminution of circulation.

Intense heat reduces or abolishes the reaction,⁹ but in 2 patients with gangrene, tested both at ward temperature and after their legs had been warmed in a cabinet, the reactions showed no noteworthy difference.

Change of position causes marked change in velocity of whealing. All subjects must be tested in the horizontal position or the results are not comparable.

The velocity of whealing on the forearm was determined before, during, and after the increase of blood pressure caused by subcutaneous injection of adrenalin (four subjects), and its decrease by inhalation of amyl nitrite (three subjects). The changes found were not significant for this investigation.

If histamin is pricked into an abnormal area of skin the reaction may be abnormal.¹⁰ Scar tissue may give no reaction. In the presence of subcutaneous edema the reactions may still be normal.

The Histamin Reaction in Nondiabetic Arteriosclerosis With and Without Hypertension. Of 11 cases of marked arteriosclerosis with hypertension 8 showed normal reactions to histamin on their feet and legs; in 1 the reaction on both feet was of Grade II; in 2 others the reaction on one foot was of Grade II, the reaction on the other foot being normal. Two cases which exhibited normal histamin reactions when their blood pressure was 205/40 and 190/115, showed neither wheal nor flare after heart failure had caused the blood pressure to fall to 110/70 and 60/50. Another case with normal reactions on admission when the blood pressure was 180/98, exhibited reactions of Grade II on one foot, Grade III on the other when, after three weeks in the hospital without special treatment, his blood pressure had fallen to 130/85. Three months later he was

much stronger, his blood pressure was 180/110 and the histamin reactions had returned to normal.

Of 7 cases of marked arteriosclerosis without hypertension only 2 showed normal reactions on their feet, in 2 the reactions were of Grade II, in 3 the wheal and flare failed to appear on one or both feet. The reactions above the knees were always normal. Two cases of hypertension without sclerosis showed normal reactions.

These results plainly suggest that arteriosclerosis causes diminution of the histamin reaction on the feet and that an increase in systemic blood pressure by compensating for the sclerotic changes in the arteries may restore the response to normal. This must be remembered in evaluating the results on diabetics.

The Histamin Reaction in Heart Disease. Six cases of valvular heart disease without decompensation (rheumatic mitral and aortic valvulitis, and syphilitic aortic valvulitis) showed normal histamin reactions.

Six cases of cardiac decompensation were studied, the test being repeated as their condition changed. When decompensation was slight the tests were within normal limits even though some edema was present. In severe decompensation the reactions on the feet became delayed, those above the knee remaining normal; *in extremis* all reactions lacked both wheal and flare.

A case of paroxysmal tachycardia gave a Grade III reaction on one foot, Grade II on the other when the pulse rate was 144, the blood pressure 93/70; a few days later when the pulse rate was 64 and the blood pressure 100/58, the reactions were normal.

From these results it is evident that cardiac failure may produce change in the histamin reaction by altering the circulation to the feet and this may be a factor in the results on certain diabetics with cardiac complications. But as cardiac disease does not change the reaction until after signs of serious trouble are obvious, the condition of the heart is not to be considered a factor in the results obtained upon the other diabetics.

The Histamin Reactions in Moribund Conditions. Histamin has been pricked into the skin of 5 moribund patients. The reactions were highly abnormal all along the leg, usually neither wheal nor flare developed. Necropsy was performed in 2 cases and no arteriosclerosis was demonstrated. It is evident that abnormality of reaction may be caused by general circulatory collapse in the absence of peripheral vascular disease.

Histamin Reaction in Peripheral Neuritis and After Peripheral Nerve Injury. Immediately after section of a peripheral nerve the skin supplied reacts normally to histamin; after degeneration of the nerve the skin wheals normally but no flare appears.¹¹ Similarly in 2 cases of peripheral neuritis the skin in the involved areas whealed normally but never flared. In a case of traumatic injury to the brachial plexus the reaction in the involved area lacked a

flare also. In 2 cases of transverse myelitis the histamin reactions above and below the level of disturbed sensation showed no significant difference. Therefore the presence of a good wheal but no flare is evidence of degeneration of certain peripheral nerves supplying the part tested.

The Circulation of the Feet in Diabetes. *Repeated Estimations in the Same Individual.* The histamin reaction has been elicited repeatedly on the same day or on successive days on normal subjects and on stabilized diabetics without noteworthy variation. But marked change in the general condition may be accompanied by corresponding change in the circulation to the feet. Examples of this have been found in certain cases of severe acidosis, during recovery from the incision of a carbuncle, and on the improvement of a concurrent disease (pulmonary tuberculosis). Some cases of severe reduction of the circulation show improvement under treatment without notable change in their diabetic condition. These cases are of sufficient importance to warrant their description in more detail together with cases in which marked change in their general condition was not accompanied by change in the circulation of the feet.

(a) *In Acidosis and on Recovery From It.* Five patients were tested during severe acidosis and after recovery from it. All gave evidence of decreased circulation in the feet during the acidosis, after this had been abolished the circulation of some cases returned to normal, in others it remained at its previous low level.

J. S. (Table II) and A. C. (Table III) were known to have had diabetes for one and one and a half years respectively. Neither had any evidence of arteriosclerosis. Recovery from the acidosis was accompanied by great improvement in the circulation to the feet.

On the other hand J. H. (Table II) had advanced arteriosclerosis. Calorimetric determinations were made every few days until the acidosis was under control. The results show that no permanent improvement of the circulation took place. On one day (April 24) soreness developed under a callus on his left foot around which a reddened area appeared. On this day the circulation was greater, but still below normal in both feet. The soreness had disappeared by the time of the next test and the flows fell to their original low level. In patient C. P. (Table III) the histamin reactions show a similar situation. This patient was arteriosclerotic and was in severe acidosis when first tested. A second test made after the acidosis had disappeared showed a worse circulation than the first.

(b) *After the Incision of a Carbuncle.* J. J. (Table III), a mild diabetic with slight arteriosclerosis, was tested when in a weakened condition the day after the incision of a large carbuncle on the back of his neck. Marked reduction of the circulation was found. Several days later he had regained his strength and the tests showed considerable improvement in the circulation.

TABLE III.—HISTAMIN REACTIONS ON THE FEET OF PATIENTS DURING AND AFTER CERTAIN DIABETIC COMPLICATIONS. THE REACTIONS ABOVE THE KNEE WERE ALWAYS NORMAL.

Patient.	Date.	Blood pressure.	Arterio-sclerosis.	Foot.	Wheel at 2½, 5, 10, 15 minutes.	Flare at 2½, 5, 10, 15 minutes.	Remarks.
C. P. Age 38	Oct. 3 1929	90/70	Moderate	R L	OO++ OO++	OOOO OOOO	Severe acidosis, stuporous; blood CO ₂ 30 volumes, per cent. Acidosis gone.
	Oct. 10 1929	92/65	R L	OOOO OOOO	OOOO OOOO	
A. C. Age 33	Nov. 7 1928	110/55	None	R L	O++++ OOO+	OOOO OOOO	In coma; blood CO ₂ 11 volumes, per cent. Acidosis better; blood CO ₂ 41 volumes per cent.
	Nov. 13 1928	85/62	R L	O++++ O++++	O++++ O++++	
J. J. Age 57	April 22 1929	135/75	Slight	R L	OOOO OOOO	OOOO OOOO	Carbuncle on back of neck incised April 21. Weak. Feeling better; stronger.
	April 25 1929	135/85	R L	OO++ OO++	OOOO OOOO	
N. S. Age 18	May 10 1928	100/62	None	R L	OO++ OO++	OO++ OO++	Active pul. tuberculosis; fever at night. Afebrile; has gained 40 pounds in weight.
	Oct. 10 1928	118/75	R L	O++++ O++++	+++++ +++++	

(c) *In Complicating Pulmonary Tuberculosis.* In 2 cases (A. B. and N. S., Table III) the diabetes was complicated by active pulmonary tuberculosis. Both were very weak and the tests showed slight reduction of the circulation in the feet. Some months later, after the tuberculosis had become inactive and they had gained weight and strength, the circulation returned to normal.

(d) *In Gangrene.* As most of the cases of gangrene were promptly operated upon, the opportunity to follow their circulation over long periods of time was infrequent. Two cases (P. K. and L. B., Figs. 3 and 4) have been secured. The improvement in the response to histamin coincident with recovery from gangrene is evident.

From these results it is obvious that the circulation of the feet may change considerably *pari passu* with fluctuations in pathologic conditions affecting the general or local circulation. But since rapid changes of significant magnitude do not occur if the diabetes is under control, it seemed of interest to determine the state of the circulation in the feet in a series of 100 consecutive cases whose condition had been stabilized by supervision in the wards and outpatient department of the University Hospital. A few cases previously referred to³ have been included in this series.

The Response to Histamin on the Lower Extremities of 100 Stabilized Diabetics. The cases have been divided into three groups according to the response to histamin. In 32 cases the histamin reaction indicated a normal circulation in both feet (Group I). In 34 the reaction was of Grade II in one or both legs, indicating slight

diminution of the circulation (Group II). In 34 cases the reaction was of Grade III on one or both feet indicating marked diminution of the circulation (Group III). The almost equal size of the groups is accidental.

In Table IV the statistical data of certain clinical features of these groups are set forth. In Group I only 1 patient has had trouble with the feet: M. T. had ulceration following a burn which healed in a month. The tests were made over a year later. The dorsalis pedis pulse was present throughout the group and only 5 patients exhibited evidence of sclerosis of the peripheral arteries. Three of these had marked hypertension. Group II obviously occupies the intermediate position. One case had serious trouble with the feet at the time of testing and is reported in detail in Fig. 2. No others had any trouble with their feet nor history of it. The average blood pressure is lower than in Group I and this is perhaps a factor in the reduced circulation to the feet. Judging from the number of cases on insulin the diabetes is more severe than in the other group; on the other hand the high average carbohydrate in the prescribed diet is caused by a number of mild cases who were doing well with but little restriction of carbohydrates.

The patients of Group III are older, have had diabetes longer, and have more evidence of arteriosclerosis than the others. In this group occur the great majority of instances of serious trouble with the feet: 5 patients had gangrene at the time of testing; 2 had had gangrene several years previously but had recovered without amputation; 2 more had had their other leg amputated for gangrene; and 2 more had indolent ulcers when tested.

These results suggest that the patient with a markedly delayed or incomplete histamin reaction on his feet has a much larger chance of serious trouble with his feet than when the reaction is more normal. But before the prognostic value of the test can be discussed it is desirable to make a more detailed analysis of the series.

A consideration of the reaction of the skin of the dorsum of the feet to histamin, of the condition of the principal artery supplying the area tested, and of the evidence of generalized arteriosclerosis makes it possible to analyze further the vascular conditions in the feet of any patient. Thus evidence can be secured that compensation for a sclerosis of the supplying vessels has occurred, the reaction of the minute vessels being normal. On the other hand evidence of disease in the minute vessels may be obtained when there is no demonstrable change in the larger. Also in some cases evidence is found that the local vasomotor reflexes do not function though the circulation may be but little reduced.

Therefore it is of interest to arrange the 100 diabetics according to the amount of general arteriosclerosis, the condition of the dorsalis pedis, and the histamin reaction on the dorsum of the foot; and to study the cases composing the different groups in order to throw

TABLE IV.—COMPARISON OF CONDITION OF CIRCULATION TO THE FEET WITH OTHER DATA IN 100 STABILIZED DIABETICS.

	Number in group.	Average age.	Average blood pressure, mm. Hg.	Number of cases with dorsalis pedis pulse of strength given.			Number of cases with sclerosis of peripheral arteries of degree given.			Average known duration of dia- betes in years.	Number of cases receiving insulin.	Average insulin dosage of cases on it in units per day.	Average carbohydrate of pre- scribed diet in grams per day.	Number of cases with gangrene or persistent infections of feet, or history of such trouble.
				Normal.	Weak.	Absent.	Slight.	Moderate.	Marked.					
Group I. Normal circulation. Hista- min reactions, Grade I	32	44	137/80	30	2	0	3	2	0	4.9	8	28	88	0
Group II. Slight diminution of circu- lation. Histamin reactions, Grade II	34	44	128/74	25	4	5	4	2	2	4.1	21	32	102	1
Group III. Marked diminution of circu- lation. Histamin reactions, Grade III	34	55	143/74	18	2	14	8	3	4	6.0	15	38	92	10

light on the clinical value of this new type of evidence. Therefore, the 100 cases have been divided into nine groups, containing the combinations of findings encountered; and a tenth group set apart for special study.

In judging the degree of general arteriosclerosis chief reliance was placed on the condition of the palpable peripheral arteries. In the ward cases additional evidence was secured by observing the retinal arteries and by demonstrating arterial calcification by Roentgen ray.

1. *No Demonstrated Arteriosclerosis—Dorsalis Pedis Pulse Strong.* (1a) *Histamin Reactions Normal.* This is the normal situation. Twenty-five cases fall into it. The average age is forty-two, the oldest sixty-nine years. The average duration of diabetes is five years. Only 3 are receiving insulin, so that the majority are mild diabetics. No one has had trouble with the feet. One aged fifty-nine years has a blood pressure of 165/100.

(1b) *Histamin Reactions Slightly Delayed (Grade II).* This may be thought of as indicating slight pathologic change in the minute vessels but the change in the histamin reaction is but little beyond the limit of technical error. Of the seventeen cases in this group 11 are receiving insulin, so the diabetes is more severe than in the preceding group. None has had trouble with the feet. Two cases have blood pressure of 170/90 and 175/85.

(1c) *Histamin Reactions Markedly Delayed (Grade III).* This combination provides evidence of change in the minute vessels of the feet without conspicuous lesions of the larger arteries. But the change, whatever its nature, extends up the leg a variable distance but cannot be demonstrated above the knee, the histamin reactions there being normal. A similar situation is sometimes found in certain decompensated cardiacs, but there is nothing to make one suspect the heart in these diabetics. There may be more sclerosis of larger arteries present than was detected by the usual examinations, but there can be no doubt about the presence of a good dorsalis pedis pulse.

In 1 case (M. B.) both the histamin tests and calorimetric determinations (Table I) were made; the low caloric output found indicates that a real diminution of bloodflow must have taken place. In another stabilized diabetic (MacM., Table I) no histamin reactions were elicited, but the low caloric output of his feet and the absence of evidence of sclerosis places him in this group.

No certain interpretation of these findings can be made. The underlying cause may be a functional constriction of arterioles, or sclerotic changes involving primarily the small arteries, or unrecognized cardiac weakness.

Eight cases are found in the group, their average age is forty-eight and they have had diabetes an average of 6.1 years. Four are taking insulin, 3 of these are on large doses, over 40 units per

day. None have hypertension, none have had trouble with their feet. The later history of this group will be followed with much interest.

2. *Generalized Arteriosclerosis Without Obliteration of Dorsalis Pedis Pulse.* (2a) *Histamin Reactions Normal.* This indicates that compensatory processes have overcome difficulties caused by the sclerotic changes. Five cases fall into this group. Four have blood pressures of 210/85, 210/85, 180/100 and 152/82 mm. of Hg., the last with but slight sclerosis has a blood pressure of 125/75. The relation of the hypertension to the compensation is evident. No case had trouble with the feet.

(2b) *Histamin Reactions Grade II.* Here compensation is not quite complete. Nine cases fall into this group, 2 had slight hypertension (166/84 and 162/88). One of these had gangrene; the reactions are shown in Fig. 2 and a detailed history is appended. This case had the best histamin reactions of any case of gangrene tested and the lesion was doing well when she died suddenly, apparently from embolism from a complicating phlebitis.

(2c) *Histamin Reaction Grade III.* In these cases a marked failure of compensation is indicated, the chief lesion being located distal to the place where the arteries can be palpated. There are 11 cases in this group, 5 had hypertension of over 160 mm. Hg. Two cases (P. K. and L. B.) had gangrene at the time of testing; their reactions are shown in Figs. 2 and 3. Both recovered without amputation. Two others had had gangrene two or three years before, one recovered without amputation, the other had a toe amputated and the foot looks well at present. The ability of the patients of this group to recover from gangrene is striking. The feet of the remainder had no acute lesions.

3. *Generalized Vascular Sclerosis, Obliteration of Dorsalis Pedis Pulse.* (3a) *Histamin Reactions Normal.* This would indicate complete compensation. No case completely filling these requirements occurs in the series. Two approach it, in one the dorsalis pedis pulse was recorded as doubtful, in the other it was just palpable. Neither had hypertension. The feet of these patients were in good condition. The development of new vascular pathways is the probable method of compensation.

(3b) *Histamin Reactions Grade II.* This indicates partial compensation. Nine cases present these findings; none had hypertension nor trouble with their feet.

(3c) *Histamin Reactions Grade III.* This indicates a marked failure of compensation and the clinical data supports this conception. Of the 13 patients in this group over one-half have or have had serious trouble with their feet. Three of these had gangrene when they were tested, 2 came to amputation, the other refused and soon died. Two cases had suffered amputation of the other leg for gangrene. Two patients had indolent infections at the time

of the examination. In 2 cases blood pressures of 230/80 and 260/95 were insufficient to compensate for the vascular lesions. That all the members of this group are in a hazardous situation seems an obvious conclusion. The reactions in 2 cases are shown in Figs. 1 and 5.

4. *Cases with the Histamin Reaction Consisting of a Good Wheal but No Flare.* The 13 cases gathered together under this heading have been included in the preceding groups but deserve special attention. This type of reaction is characteristic of degeneration of peripheral nerves.¹¹ However I have seen it in a moribund cardiac case who previously had given normal reactions and again in a comatose diabetic (A. C., Table III) who gave normal reactions after the acidosis had been overcome. The cause of disappearance of the local vasomotor reflexes in these cases is not clear.

It must be remembered that when the lack of adequate circulation abolishes both wheal and flare the histamin reaction throws no light on the condition of the peripheral vasomotor reflexes, for they may be present without being demonstrable. No certain division can be made between cases failing to exhibit a flare because of diminished circulation and those in whom its appearance is prevented by degeneration of peripheral nerves; and both conditions may occur together. But when the wheal always appears promptly and becomes well developed and no flare follows, degeneration of the peripheral nerves should certainly be suspected, and it is of interest to examine certain clinical characteristics of the group of diabetics showing this type of reaction.

In 2 cases the wheal appeared within five minutes but no flare followed. In 11 cases the wheal was absent at five but appeared within ten minutes and became well developed, suggesting a disappearance of the reflex together with some diminution of the circulation. Five of the 13 exhibited numbness and paræsthesias which led to the clinical diagnosis of peripheral neuritis by the physician in charge, in the remainder this condition was not suspected. A surprisingly large percentage have had trouble with their feet, 3 had gangrene at the time of testing (J. K., Fig. 5 and P. K., Fig. 3 are in this group). Another (L. B., Fig. 4) exhibited this type of reaction after recovery from gangrene, another had previously suffered amputation of the other leg. The group as a whole suggests that a lack of vasomotor response may be a factor in the development of gangrene which deserves more attention. The lack of resistance to infection seen in other nervous diseases is perhaps analogous.

Histamin Reactions on Patients with Gangrene of the Feet. The reactions have been elicited in 14 patients with gangrene of the feet; in 2 the lesions were bilateral. Eight of these patients were seen after the series of 100 cases had been completed. Twelve had diabetes, the remainder were diagnosed arteriosclerosis. The findings

on 5 of the diabetics are pictured in the figures. In all cases the diabetes was easily controlled and the urine and blood sugar became normal within a few days after admission. The legs were placed in a cabinet or bed tent warmed by electric light bulbs, the lesions were lightly dressed.

EXPLANATION OF FIGURES.

The histamin reactions are indicated diagrammatically, and are in scale with the ruled centimeter in the upper left-hand corner. The tests were placed on the anterior aspect of the leg at the level indicated by the relation to the leg diagram. The number indicates the time in minutes after the introduction of histamin. Small dotted circles indicate red spots, the much larger dotted circles indicate the outline of flares. (No attempt has been made to indicate the speckled appearance of some flares.) Wheals are outlined by a solid line, the number of cross hatches indicating height.

The presence or absence of arterial pulsation is indicated by a + or - sign located at the level of the artery on the leg diagram. The letter *P* indicates pain not associated with movement; *C* indicates pain associated with movement (intermittent claudication); *S* indicates disturbance of sensation; these letters are located near the spot where the sensation was felt. Areas of gangrene or of acute inflammation have been shaded.

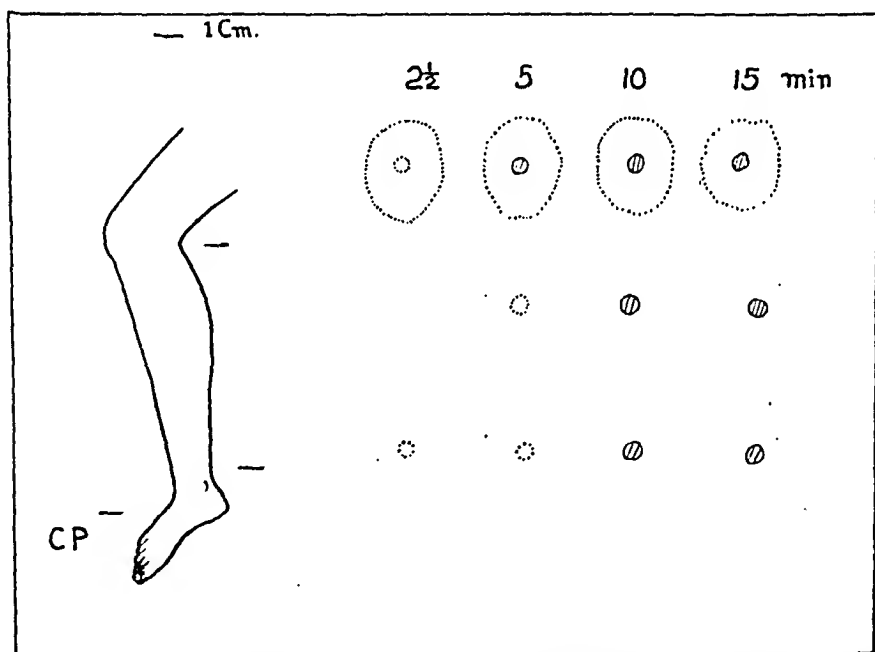


Fig. 1.—J. H., aged fifty-nine years. Diabetes mellitus just diagnosed, foot painful for four months. Foot becomes blue when in dependent position, blanched when elevated. A red flush extended half way over the dorsum, histamin was pricked into this but no response could be seen. Moderate generalized arteriosclerosis. Roentgen ray showed calcification in the arteries of both legs. Auricular fibrillation. Blood pressure 230-130/80. Gangrene of tip of second toe seven days after the tests. Amputation at junction of middle and lower thirds of thigh. Healing of stump satisfactory. Patient died suddenly six weeks after discharge from hospital. No necropsy.

The histamin reactions pictured in Fig. 1 represent the most common finding except that on the dorsum of the foot a red spot is usually seen. Normal reactions occurring only above the knee

occurred in twelve of the sixteen legs with gangrene of the feet. This finding suggests a reason for the surgical experience that amputation below the knee is usually unsuccessful.

The other types of reaction found are illustrated in Figs. 2 to 5. They will be discussed later.

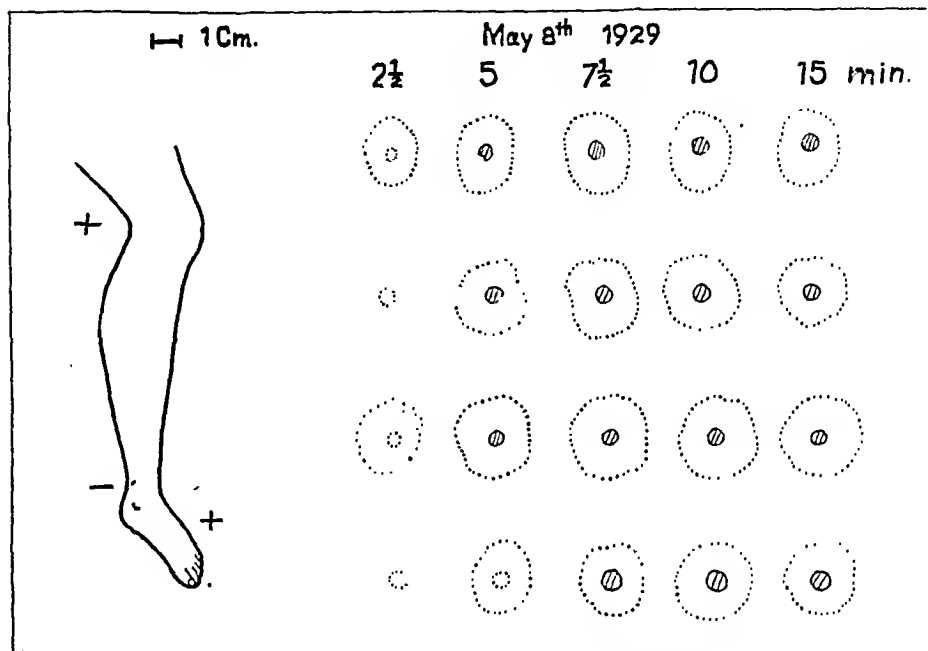


FIG. 2.—E. A., aged forty-one years. Diabetes mellitus for fourteen years. Ulcer under ball of foot for three months, gangrenous spot developed a week before admission with red streaks extending up leg. Slight arterial calcification by Roentgen ray. Foot did well until three days after testing when pain developed in calf, later in popliteal space. Sudden collapse and death two days later. Necropsy not permitted.

Discussion. When histamin reactions are elicited on the feet in the manner prescribed the causes of diminished vascular response can be grouped under two principal headings. First, that due to peripheral vascular disease and characterized by normal responses on the thigh becoming progressively more abnormal down the leg. A second type is to be attributed to cardiac weakness and its accompanying vasoconstriction; in extreme cases it is characterized by abnormal reactions all along the leg, when the condition is less marked by reactions much similar to those seen in peripheral vascular disease. Patients moribund from a variety of causes have shown this type. However, as many cases of mild cardiac decompensation show normal reactions, the cardiac type of reduced reactions is to be expected only when the clinical picture is obvious.

Both of these types may occur together. In patients with peripheral vascular disease marked rapid fluctuations in the general condition have been accompanied by corresponding changes in the

reactions on the feet. Such observations provide evidence that the circulation in the extremities may be increased by an improvement in the patient's general condition; they illustrate a principle underlying the conservative treatment of pedal lesions.

Both the histamin reaction and the studies of caloric output indicate that the majority of diabetics have a subnormal circulation in their feet. Morrison and Bogen¹² found that arterial calcification could be demonstrated by Roentgen ray in 53 per cent of 324 unselected diabetics. At necropsy arteriosclerosis is found in 79 per cent

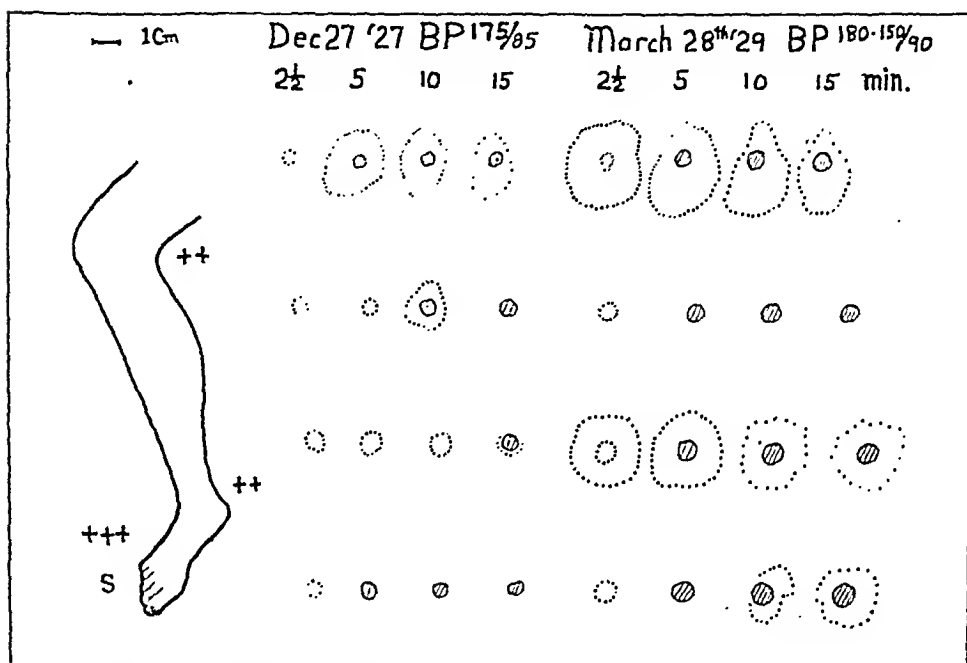


FIG. 3.—P. K., aged sixty-five years. Diabetes mellitus for eighteen years. Sore toe since 1925. Admitted November 26, 1927. First and second toes reddened, swollen, insensitive, pus exudes from below a callus. Bullæ on great toes. Roentgen ray showed loss of substance of terminal phalanx of right great toe with rarefaction of all bones of feet, also considerable calcification in vessels of feet and legs. Very marked arteriosclerosis of all palpable vessels. Paroxysmal auricular tachycardia with slight cardiac decompensation. Discharged February 22, 1928. Readmitted March, 1929. Auricular fibrillation. Lesions of foot healed, only some redness of toes remaining.

of the diabetics in Joslin's series.¹³ A case of diabetes and one of arteriosclerotic gangrene tested by Stewart¹⁴ gave a low caloric output in both the gangrenous and the normal foot. Therefore, our results are consistent with other knowledge on the subject and are a demonstration of the feeble cutaneous circulation in diabetes long recognized by clinicians.

Taking the results as a whole there is general correspondence between the clinical examination of the feet and the reaction of the skin of the feet to histamin. The same general agreement is seen between the physical findings and the caloric output (Table I).

Therefore in many cases these tests provide only confirmatory evidence of a normal or pathologic condition of the circulation in the feet. But the results recorded in Table I indicate that a considerable reduction in the circulation may occur without the development of any physical signs and that their full development occurs only when reduction is extreme.

But as soon as individual patients are studied it is seen that the histamin reaction will at times detect change in the circulatory responses when they would not otherwise be suspected, and will demonstrate normal conditions in the minute vessels when the

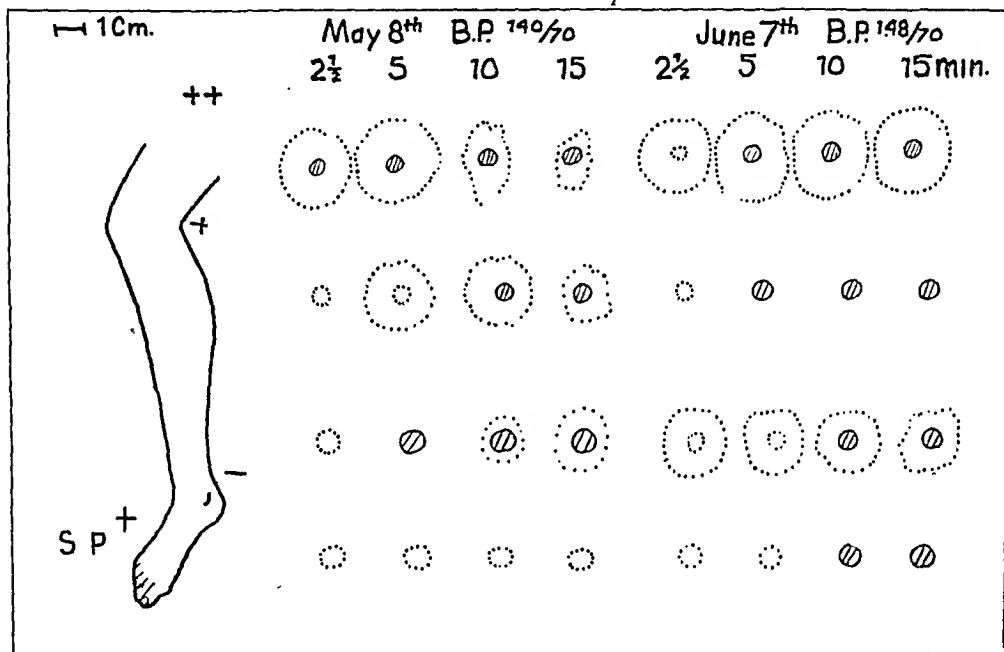


FIG. 4.—L. B., aged fifty-seven years. Diabetes mellitus for fourteen years. Toes sore for six weeks. On admission April 29, 1929 gangrenous ulcer on middle toe surrounded by inflamed area. Great toe also inflamed. Numbness and paresthesias of entire foot. Slight edema to ankle, Roentgen ray showed marked absorption of terminal phalanx of middle toe, and some calcification of dorsalis pedis arteries. Toes healed by May 30, 1929. Paresthesias remained.

physical examination indicates arterial disease. The calorimetric studies also show these two types. Therefore the histamin reaction together with the physical examination permits the easy clinical demonstration of certain conditions long recognized in the pathologic literature, but not associated with individual patients nor made the basis for prognosis and treatment. Thus, it is easy to determine whether the compensatory changes, as rise in general blood pressure and development of new blood paths, have overcome the handicap of a sclerotic main artery. In other cases evidence of abnormal vascular responses without demonstrable sclerosis of larger vessels suggests pathologic change beginning peripherally, and arterio-

sclerosis of this type is not uncommon.¹⁵ In some cases evidence of failure of local vasomotor reflex responses may be secured. Thus the histamin reaction supplements the physical examination, the former demonstrating the physiologic conditions in the minute vessels, the latter providing information concerning the larger arteries.

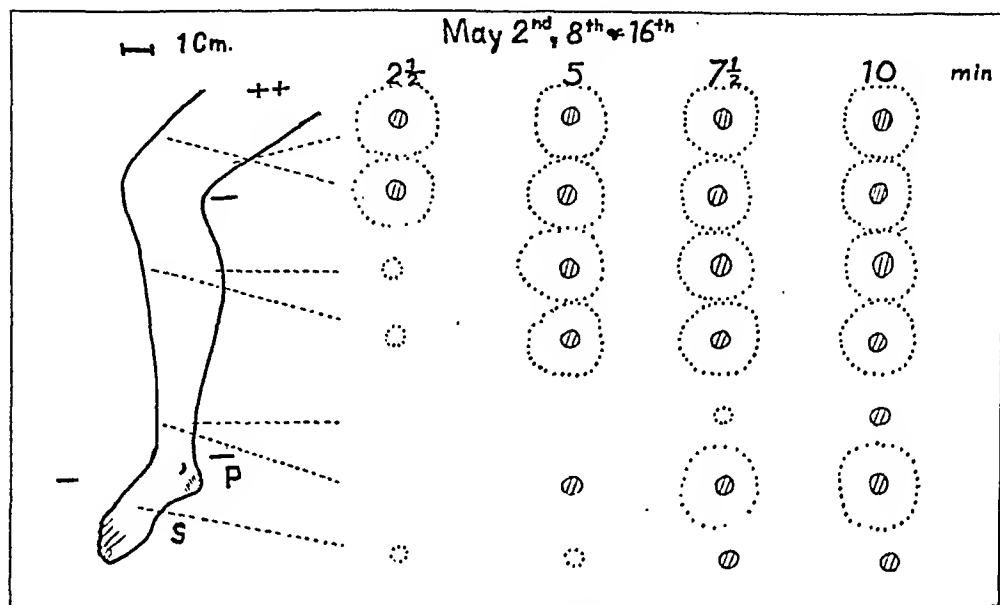


FIG. 5.—Histamin reactions on anterior and posterior aspects of leg as indicated by dotted lines. J. K., aged sixty-six years. Diabetes mellitus for eight years. Heel sore for about three weeks. On admission April 30, 1929, large ulcer with gangrenous margins extending down to os calcis, lower part of leg somewhat wasted, paresthesias over right foot. Râles at lung bases. Retention of urine, blood-urea nitrogen 31 mg. per 100 cc. Slight evening fever. Blood pressure 130/57. Roentgen ray showed tuberculous infiltration of both apices probably active, also calcification in leg arteries. No tubercle bacilli found in sputum. Conservative treatment until May 18, 1929, caused improvement in râles, normal blood-urea nitrogen, slightly less fever; pain persisted, no improvement in gangrene, nor change in histamin reactions.

Amputation May 18, 1929, 8 inches below tibial tubercle. Convalescence stormy, healing of stump delayed. Discharged June 17, 1929, with stump almost healed. July 7, 1929, stump reported healed, August 23, 1929, reported to be getting about on peg leg. January 3, 1930, working, getting about on peg leg, there is an area the size of a match head on stump which is dressed daily; not under care of physician.

Pathologic report on vessels of stump. Grossly anterior tibial essentially normal lumen open, wall possibly a little thick. Posterior tibial small and thickened and a lumen was demonstrated only in the upper portion. Sections confirmatory. Diagnosis endarteritis obliterans of posterior tibial.

It is obvious that data on the 100 diabetics have not been in existence long enough to determine finally their prognostic significance; but several features should be pointed out. The group of cases showing generalized arteriosclerosis with obliteration of dorsalis pedis pulsation and a Grade III histamin reaction contains over 50 per cent of cases with serious trouble with their feet; the situation of patients showing these findings must be regarded as hazardous. The group of cases with generalized arteriosclerosis, a Grade III

histamin reaction, but with a palpable dorsalis pedis pulse also shows a high percentage of trouble, but the number of recoveries without amputation is striking. In contrast to these, the cases with normal histamin reactions show almost complete freedom from trouble with their feet and it would appear that these cases had little to fear from this complication. Attempts at making a prognosis for patients in the intermediate groups had best be suspended until more time has elapsed. The results show one thing clearly, a consideration of both the physical examination and the histamin reaction gives far better indication of the incidence of trouble with the feet than does a consideration of either alone.

In considering the group of cases in which gangrene has already occurred one finds that this condition is usually accompanied by profound alterations in all histamin reactions below the knee, but that gangrene may occur with but little reduction in the reactions. Cases of gangrene when the usual signs of diminished circulation are absent have been reported by others.¹⁶

In considering the usefulness of the histamin reaction in determining the course of treatment several facts should be pointed out. The histamin reaction can be improved by treatment. A Grade III reaction in a patient with gangrene of the foot does not demand amputation, both gangrene and reaction may improve together.

However a study of the series leaves one with certain definite impressions. Patients with a Grade III histamin reaction on the foot and a good dorsalis pedis pulse have often recovered from gangrene without amputation; in those with similar reactions but with no pulsation in the dorsalis pedis conservative treatment has not been successful. Patients with no complete histamin reactions below the knee have usually come to high amputation or died. Improvement in the reactions after a period of conservative treatment is encouraging, lack of it discouraging. The prognostic significance of the disappearance of the vasomotor reflexes cannot be evaluated from the data now at hand.

In discussing the value of the histamin reactions in choosing the level of amputation certain considerations must be emphasized. A blood supply which perfectly suffices for the nutrition of a limb may be insufficient to ensure cicatrization of a stump.¹⁷ The process of healing is to be thought of as demanding hypertrophy and hyperplasia of the vascular bed with an increased blood supply. Therefore the decision regarding level of amputation should be based not only on the circulatory conditions present before amputation but also upon an estimate of the possibility of increase of circulation. While no criteria exist on which this estimation can be based with certainty, the age and strength of the patient, the duration of the disease, the condition of the heart, vessels, and blood pressure are to be thought of as factors, as well as local vascular conditions.

An abnormal histamin reaction indicating imperfect compensa-

tion would seem to offer a poor chance of successful healing of a stump at that level; no amputation has been advised where the reactions were abnormal. On the other hand normal conditions in minute vessels may have been attained by a maximum of circulatory compensation, and the increase necessary to heal a stump may not be possible. However, as many elderly patients never walk after amputations above the knee and as lower amputations are at times successful, it seems legitimate to attempt this procedure where the histamin reaction is normal, the condition of the large arteries satisfactory, and the general condition good. An amputation below the knee was performed on one of our cases of diabetic gangrene which partly met these conditions and while healing was delayed, a stump was eventually secured which has been supporting an artificial leg for six months. To summarize, an abnormal histamin reaction appears to us to contraindicate amputation at that level, but a normal reaction is no guarantee of success. That this conclusion is based on reasoning rather than on the data must be emphasized; data on this point will accumulate but slowly.

Summary and Conclusions. In a series of 100 unselected diabetics under treatment the response of the skin of the lower extremities to histamin under standard conditions indicated that 32 per cent had a normal circulation in their feet, in 34 per cent the circulation was somewhat impaired, in 34 per cent markedly impaired. The caloric output of the feet was determined thirty times in 8 diabetics; it was constantly below normal in 6 patients. It is concluded that the majority of diabetics have an abnormally low bloodflow through their feet.

The circulation in the feet of certain diabetics may vary markedly with their general condition, but in certain arteriosclerotic diabetics improvement in general condition is not followed by improvement in circulation to the feet. In certain arteriosclerotic individuals the height of the general blood pressure has a marked influence on the circulation to the feet.

The reaction of the skin of the feet to histamin together with the physical findings permits the demonstration of the presence or absence of adaptations to compensate for sclerotic narrowing of the large arteries, and allows the clinical detection of pathologic change in the minute vessels when the larger arteries are not notably involved. In certain cases the presence or absence of local vasomotor reflex responses can be demonstrated.

Such demonstrations permit the assignment of individual cases to one of a number of groups. The great majority of patients with trouble with their feet or history of it fall into two groups characterized by markedly abnormal histamin reactions and generalized arteriosclerotic changes. The data plainly imply that by considering the histamin reaction together with the physical findings a more accurate prognosis can be made than by considering either separately.

The types of histamin reaction occurring on the legs of 14 patients with gangrene of the feet are described. The value of this evidence in aiding the selection of treatment and choosing the level of amputation is discussed.

BIBLIOGRAPHY.

1. Stewart, G. N.: Studies on the Circulation in Man, I, Heart, 1911-1912, 3, 33; and VII, J. Exper. Med., 1913, 18, 354.
2. Lewis, T.: The Bloodvessels of the Human Skin and their Responses, London, Shaw & Sons, 1927, Chapters V and VIII.
3. Starr, I., Jr.: Change in the Reaction of the Skin to Histamin, as Evidence of Deficient Circulation in the Lower Extremities, J. Am. Med. Assn., 1928, 90, 2092.
4. Harris, K. E., and Marvin, H. M.: Heart, 1927, 14, 49.
5. Stewart, G. N.: Studies on the Circulation in Man, The Harvey Lectures, Philadelphia, J. B. Lippincott Company, 1912-1913, p. 36.
6. Sheard, C.: Calorimetric Studies of the Extremities, J. Clin. Inv., 1926-1927, 3, 327.
7. Stewart, G. N.: Studies on the Circulation in Man, VII and VIII; J. Exper. Med., 1913, 18, 354, 389.
8. Lewis, T.: Reference 2, especially Chapters V and VI.
9. Lewis, T.: Reference 2, Chapter VII.
10. Lewis, T.: Reference 2, Chapters VIII and IX.
11. Lewis, T.: Reference 2, Chapter V.
12. Morrison, L. B., and Bogen, I. K.: J. Am. Med. Assn., 1929, 92, 1424.
13. Joslin, E. C.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928, p. 678.
14. Stewart, G. N.: Reference 5, page 140.
15. Jores, L.: in Henke, F. and Lubarsch, O.: Handbuch der Speziellen Pathologischen Anatomie und Histologie, II, Berlin, J. Springer, 1924, p. 709.
16. Buerger, L.: The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924, p. 427.
17. Leibovici, R.: J. de Chir., 1929, 34, 293.

NORMAL URINE SUGAR IN CYSTOSCOPIC EXAMINATIONS.

BY RUSSELL RICHARDSON, M.D.,

ASSOCIATE IN MEDICINE AT THE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,
AND DIRECTOR OF THE LABORATORY OF THE METHODIST EPISCOPAL HOSPITAL,

AND

RUTH S. BITTER

PHILADELPHIA.

(From the Laboratory of the Methodist Episcopal Hospital.)

THE presence of a reducing substance in normal urine has been recognized since Pavy, in 1899, held that the kidneys were permeable to small traces of what he thought to be dextrose. Its character and origin, however, are still a matter of discussion. Folin and Berglund¹ and Eagle² believe that it is made up of carbohydrates, not dextrose, which are taken in with the food, and which the body is unable to utilize. Greenwald, Gross and Samet³ give it a double origin; according to Folin, partly from the metabolization of pro-

tein, and, more recently, possibly from carbohydrates formed by intestinal bacteria. Benedict,⁴ on the other hand, thinks that it is partly dextrose which has escaped through the kidneys in small amounts from a normal blood sugar. The presence and amount of this substance in the blood are still undetermined, due to inclusion of it, if present, in the regular quantitative methods for blood sugar. Hubbard and Allison⁵ have recently pointed out that, if the blood filtrate according to Folin and Wu be fermented with *B. coli*, and the reduction then determined, there is found a small residue of non-fermentable material which may have some connection with this reducing substance in the urine. In this work we shall speak of this reducing substance as sugar, as it appears that some of it, at least, is carbohydrate.

We have been interested in this sugar from a different angle; namely, the ability of the kidneys to excrete it in health and disease. We wish to report at this time on the results of sugar determinations on urines procured from both kidneys by ureteral catheterization done during cystoscopic examinations. These examinations were made in the course of studying patients who presented symptoms pointing to a lesion in one or the other kidney. The specimens were collected in the customary manner and were sent to the laboratory for routine examination, and culture and guinea-pig inoculation. We have used paired specimens because, as we felt that there was still too much uncertainty regarding this sugar in the blood, it seemed that a comparison of urines from a normal and a damaged kidney, both excreting from the same blood, would make possible a more definite study.

The method used for determining the urine sugar was that of Folin⁶ with more recent changes.⁷ This method calls for 5 cc. of urine, but on account of the small amount of urine sometimes procured in ureteral catheterization, we have adapted the method for smaller amounts. These examinations were sufficiently checked with those done on the full 5 cc. so that there is no question of their accuracy; the difference in results between the two methods was so small as to be negligible. The results are expressed in mg. per 100 cc. of urine.

It is probable that the blood reaching both kidneys is similar in composition, so that with equal function similar urines should result. In the various forms of nephritis, both kidneys are usually more or less equally affected. In the kidneys presented to the surgeon, on the other hand, there is most often a damaging affection which is unilateral. The surgeon considering operation must determine three things: (1) Which kidney is affected and by what variety of process? (2) how much the function of the damaged kidney is decreased, and (3) whether the function of the other kidney is sufficient to do the work of both if the damaged kidney is removed? We think that a study of the sugar in the specimens from both

kidneys aids in this work, especially when taken in conjunction with such accepted examinations as the phenolsulphonephthalein, indigo carmine, routine study and culture of the urine, together with the clinical findings.

In all, 96 pairs of specimens were examined and the results compared. It was not possible to determine accurately the condition in 24 cases, either because of insufficient data or because they are still under study. In 36 cases (38 per cent) the kidneys appeared to be normal in function, or at least as far as could be determined by usual urologic methods, there were no unilateral lesions which decreased the efficiency of either organ. (Table I.) In all of these the sugar excreted by both kidneys was singularly similar in amount. The amount of this sugar found in the urines of these supposedly normal kidneys varied from 9 mg. per 100 cc. of urine to 210 mg. per 100 cc. This sugar from pairs of kidneys did not differ more than 6 to 7 mg. in the higher figures, or 1 to 2 mg. in the lower. In those urines with the very high figures, qualitative tests done with Benedict's solution showed some reduction, and the patients were found to have an increased blood sugar. In other words, they were mild or potential diabetics. Some higher figures were also found following a meal. As has been pointed out, we know little of this substance in the blood, so that no attempt was made at this time to find out from what concentration in the blood the amounts in the urine were secreted. Of course, this may vary considerably. No special attention was paid to diet. In some cases there was a moderate difference in the amount of fluid excreted and possibly, therefore, in the concentration of the sugar. The collection time of urine from the two sides was usually equal and the amount of urine recovered was generally similar.

TABLE I.—CASES WITH BOTH KIDNEYS NORMAL AND HAVING EQUAL SUGAR

Case No.	Sugar in mg. per 100 cc.		Case No.	Sugar in mg. per 100 cc.	
	Left.	Right.		Left.	Right.
4 . . .	v. ft. tr.	v. ft. tr.	54 . . .	69	62
9 . . .	25	24	55 . . .	77	68
13 . . .	v. ft. tr.	v. ft. tr.	62 . . .	9	11
14 . . .	76	68	65 . . .	42	46
16 . . .	22	20	66 . . .	54	61
18 . . .	9	14	67 . . .	54	57
21 . . .	16	16	70 . . .	48	45
25 . . .	12	15	71 . . .	41*	56
32 . . .	36	31	73 . . .	26	30
33 . . .	17	17	80 . . .	20	17
34 . . .	141	138	82 . . .	90	100
35 . . .	86	80	83 . . .	144	148
37 . . .	210	204	84 . . .	112	120
44 . . .	26	23	86 . . .	ft. tr.	ft. tr.
45 . . .	11	9	90 . . .	ft. tr.	ft. tr.
46 . . .	33	38	93 . . .	106	112
47 . . .	17	17	99 . . .	42	44
48 . . .	17	17	100 . . .	ft. tr.	ft. tr.

* Accidentally diluted with salt solution during collection.

Usually only one examination was done on the cases with normal kidneys. One patient, however, was examined three times at intervals of about a week. Each time the sugar from both kidneys was very nearly equal, showing that the two normal organs apparently do not vary in function from time to time. The figures were for the first examination, left 17 mg. per 100 cc. urine, right 16 mg. per 100 cc. urine; second examination, left 20 mg., right 23 mg., and third examination, left 38 mg., right 37 mg.

The presence of a considerable number of *B. coli* in the urine without other evidence of inflammation seemed to make little or no difference in the amount of sugar excreted. These organisms were present in 6 cases when no pus or other evidences of inflammation or defective function were found. (Table II.)

TABLE II.—CASES WITH NORMAL FUNCTION AND *BACILLUS COLI* FOUND IN CULTURE FROM BOTH URINES.

Case No.	Sugar in mg. per 100 cc.		
	Left.	Right.	
5	30	30	
12	14	11	
20	16	17	
40	45	46	12.30 P.M. Apr. 1, 1929 (following lunch)
	45	45	1.00 P.M.
	38	41	1.30 P.M.
	17	19	2.00 P.M.
	21	19	2.30 P.M.
	19	17	3.00 P.M.
	25	26	3.30 P.M.
	24	24	4.00 P.M.
50	49	43	May 15, 1929
	19	18	June 11, 1929
97	34	34	

In those patients where one kidney was apparently without function we found that the corresponding urine showed no sugar, or only a trace as compared to the urine from the normal side. Several of these kidneys were removed and found to have very little functioning tissue; they usually showed a severe hydronephrosis or infection. However, where a moderate amount of apparently functioning tissue still remained, even with lesions present, such as tuberculous abscesses, sugar from the affected side was definitely present, though much less than in urine from the normal kidney. (Table III.)

There were 4 cases in which a kidney with a decreased phenol-sulphonaphthalein excretion showed a definitely higher concentration of sugar than its fellow. The first time that this occurred it was thought that there had been an error in collecting the right and left specimens. In the later cases, however, the collection was made personally and with such care that no such explanation was possible. This combination accompanied, in all 4 cases, a kidney damage that was of short duration; in 3 cases a stone with temporary ureteral

obstruction and in the fourth an acute perinephric infection of about five days' standing. A possible explanation for this seems to be indicated from the work of Richards and Wearn^{8,9} who found, in the frog, by quantitative examination, that chlorids and sugar were passed through the glomerular filter and reabsorbed by the tubules from the filtrate. We would suggest the possibility that the damaged renal tubules may have been unable to reabsorb all of the sugar from the filtrate, so that it was excreted in larger amount than from the good kidney.* Unfortunately, we did not do the chlorid determination on these specimens. However, in one case we estimated the urea nitrogen and found it to be, as the sugar, larger in amount from the damaged kidney. (Table IV.)

TABLE III.—CASES WITH ONE KIDNEY DAMAGED AND EXCRETING LESS SUGAR.

Case No.	Sugar in mg. per 100 cc.		Case No.	Sugar in mg. per 100 cc.	
	Damaged.	Normal.		Damaged.	Normal.
7 . . .	v. ft. tr.	15	68 . . .	22	45
8 . . .	None	12	74 . . .	25	35
11 . . .	7	25	77 . . .	30	53
19 . . .	19	51	78 . . .	ft. tr.	40
23 . . .	18	45	79 . . .	20	44
24 . . .	15	31	81 . . .	22	27
28 . . .	16	23	85 . . .	15	20
36 . . .	17	35	87 . . .	18	28
51 . . .	29	42	89 . . .	38	68
56 . . .	42	61	91 . . .	ft. tr.	100
58 . . .	8	49			

TABLE IV.—CASES IN WHICH THE DAMAGED KIDNEY EXCRETED MORE SUGAR.

Case No.	Sugar in mg. per 100 cc.		
	Damaged.	Normal.	
42 . . .	95	49	Ureteral stone with obstruction of short duration
57 . . .	56	40	Chronic pyelitis
63 . . .	63	42	Renal calculus
72 . . .	68	37	Acute renal and perinephric infection.

Mrs. E. O., following an acute attack of ureteral obstruction by calculus, excreted 34 per cent phenolsulphonephthalein on the normal side and 1.5 per cent on the damaged side. The sugar from the corresponding kidneys was 49 mg. and 95 mg. per 100 cc. of urine. It is also of interest that the urine urea nitrogen on the damaged side showed an increase over that from the normal kidney; namely, in 4 specimens 12 to 15 mg. on the normal side, 19 to 28 mg. from the damaged organ. After nine days of rest and treatment, during which a stone was passed, the two kidneys showed a normal phenolsulphonephthalein test and urine sugars equal in amount.

* Since the above was written there has appeared a paper by James A. Hawkins, Eaton M. MacKay and Donald D. Van Slyke (Glucose Excretion in Bright's Disease, J. Clin. Invest., 1929, 8, 107) who suggest this to account for increase of urine sugar in nephritis.

It was possible to study sections from one kidney in the urine from which this condition was found.

Case Report. CASE I.—A woman, aged twenty-eight years, came to the hospital with signs of acute infection and pain in the right loin of five days' duration. Her temperature ranged from 105° to 106° F. and the white blood cell count ran about 21,000. She had had a carbuncle of the thigh several weeks previously. All other examinations were negative. A cystoscopic examination showed 1 left and 2 right ureters opening into the bladder. It was found that the left kidney excreted a urine with good phenolsulphonephthalein concentration and sugar of 37 mg. per 100 cc. urine. The right kidney, on the other hand, excreted a urine with only a trace of phenolsulphonephthalein but with a sugar content of 68 mg. per 100 cc. of urine. It seemed that this sugar might be increased in urine from an obviously damaged kidney because the affected tubules were not able to reabsorb it from the glomerular filtrate. At operation the right kidney was found to be the center of a severe inflammatory condition in which the *Staphylococcus aureus* was present. When the kidney was removed and the region drained the patient improved greatly. Microscopic sections of the kidney showed an inflammatory reaction at the periphery to a depth of several millimeters, and beneath that a congestion of the glomeruli with red blood cells, and marked damage to the tubules, the epithelium of which showed much necrosis.

Folin and Berglund¹ have shown that following a meal this sugar in the urine rises to an amount much above that found during the post absorptive stage. It seemed to us that a slightly damaged kidney should be able to excrete an amount of this sugar equal to the normal kidney during the post absorptive stage, but that following a meal it might not be able to take care of the increased amount normally present in the blood at this time. In order to demonstrate this it was, of course, necessary to leave the catheters in place for several hours, the cystoscope however, being removed. Several patients were examined in this way, though occasionally the presence of the catheters caused too much pain to allow of continuing the examination. The following case illustrates this point:

CASE II.—P. S., male, aged forty-two years, had a recurrent stricture of the left ureter which gave considerable pain from time to time. He returned for several dilatations. The phenolsulphonephthalein excretion was equal on both sides, and normal in amount, with no leakage into the bladder. The postabsorptive sugar amounts were: left, 20 mg., and right, 21 mg. per 100 cc. of urine. One hour after a meal, with the catheters in place, the left kidney excreted 43 mg. and the right 57 mg. per 100 cc. of urine, and one hour later the left excreted 28 mg. and the right 37 mg. per 100 cc. of urine. Apparently the defective left kidney had not a reserve function equal to the right, although it seemed able to work satisfactorily when not under a strain. The same result was found in two later examinations in this patient as well as in several other patients. (Table V.)

A case of polycystic kidneys, in which there had been some local pain, showed from the left kidney 31 mg. and from the right 23 mg. sugar per 100 cc. of urine. The diagnosis was confirmed

at operation, there being "a very large polycystic kidney on the left side and a somewhat smaller polycystic kidney on the right." The phenolsulphonaphthalein examinations were normal and equal.

TABLE V.—CASE 52, SHOWING INABILITY OF DAMAGED LEFT KIDNEY TO EQUAL FUNCTION OF ITS FELLOW IN ABSORPTIVE PERIOD. FOR COMPARISON WITH THE NORMAL, SEE CASE 40, TABLE II.

Sugar.		Urea N.		
Left.	Right.	Left.	Right.	
43	57	12	18	One hour after lunch.
28	37	8	12	Two hours after lunch.
20	21	5	6	Three hours after lunch.
26	31	Four hours after lunch.

TABLE VI.—CASES IN WHICH BOTH KIDNEYS WERE DAMAGED AND PROBABLY DEFICIENT.

Case No.	Sugar in mg. per 100 cc.		Diagnosis.
	Left.	Right.	
6	52	35	Double hydronephrosis.
22	31	24	Polycystic kidneys.
26	10	11	Chronic nephritis.

Conclusions. 1. Normal urine sugars in specimens obtained by ureteral catheterization usually show approximately equal amounts of sugar from the two kidneys in the absence of any disease which damages the efficiency of either kidney.

2. Where a kidney is badly damaged the sugar is very much decreased compared with that from the normal kidney.

3. An increased sugar secretion may accompany an apparently temporary damage which is demonstrable by decreased phenolsulphonaphthalein tests.

4. A slight reduction in functional efficiency may be evident only when the kidneys are forced to excrete sugar at a higher concentration, as following a meal. The damaged kidney cannot excrete urine of as high a sugar content as its fellow.

BIBLIOGRAPHY.

1. Folin, O., and Berglund, H. J.: J. Biol. Chem., 1922, 51, 213.
2. Eagle, H. S.: J. Biol. Chem., 1926-1927, 71, 481.
3. Greenwald, I., Gross, J., and Samet, J.: J. Biol. Chem., 1924-1925, 62, 401.
4. Benedict, S. R., and Osterberg, E.: J. Biol. Chem., 1923, 60, 769.
5. Hubbard, R. S., and Allison, C. B.: Proc. Soc. Exp. Biol. and Med., 1928, 25, 408.
6. Folin, O.: J. Biol. Chem., 1926, 67, 357.
7. Folin, O., and Svedberg, A.: J. Biol. Chem., 1926, 70, 405.
8. Richards, A. N., and Wearn, J. T.: Am. J. Physiol., 1924, 71, 209.
9. Richards, A. N., and Wearn, J. T.: J. Biol. Chem., 1925, 66, 247.

DIABETIC KETOSIS AND FUNCTIONAL RENAL INSUFFICIENCY.

By ALVIN F. COBURN, M.D.,

INSTRUCTOR IN MEDICINE, COLUMBIA UNIVERSITY; RESIDENT PHYSICIAN
PRESBYTERIAN HOSPITAL.

(From the Department of Practice of Medicine, Presbyterian Hospital, and the College of Physicians and Surgeons, New York.)

NOTWITHSTANDING the use of insulin and the emphasis that has been placed on the diagnosis and treatment of diabetic coma, death continues to occur in patients with severe ketosis. In some instances a fatal outcome might be obviated if there existed greater knowledge of the difficulties which must be overcome to restore the patient to health. With this purpose, a study is made of the patients in diabetic ketosis admitted to the medical wards of the Presbyterian Hospital between 1916 and 1930.

This group, comprising approximately 132 instances of severe ketosis, that is, with marked symptoms and a blood CO_2 -combining power of less than 25 volumes per cent, may be divided into two classes: (1) 30 patients treated before 1923 without insulin, and (2), 92 instances of ketosis treated with insulin. In the first group death was usually inevitable; there were only two recoveries from ketosis. With the therapeutic measures now commonly employed, there have been twenty-seven fatalities since 1923 in the second group. Of these, eleven seemed unavoidable; that is, 6 patients died of other diseases, including lobar pneumonia, coronary occlusion, and tuberculosis. Three other patients were admitted moribund, and 2 died suddenly from unexplained causes. Sixteen patients, while being treated with insulin, died of diabetic ketosis without complication, so far as could be determined. This investigation is made to determine the factors responsible for such fatalities.

In any such study of a considerable number of cases, the variable factors concerned are many. There were certain features of striking prognostic importance, particularly the age of the patient, the duration of ketosis before admission to the hospital, and the severity of ketosis at the time of admission. These have long been known and are apparent in most studies of diabetic ketosis. There were other signs and symptoms which were extremely variable and could not be correlated, such as adiposity, vomiting, dehydration, and starvation, and the same was true of various laboratory findings; CO_2 -combining power, total base, blood and urinary acetone, blood sugar and blood fat.

There were, however, one symptom, or symptom complex, and one corresponding therapeutic procedure which in many of the more serious cases became important factors, and in some cases appar-

ently deciding factors in the ultimate outcome. This symptom complex was renal insufficiency, with particular reference to the excretion of acetone bodies; and the procedure which alleviated it was the intravenous infusions of large amounts of fluid.

The importance of the symptom complex of renal insufficiency and the effectiveness of intravenous fluids became apparent in the following way:

(a) In accordance with the accepted practice of the time, the group of pre-insulin ketoses were all treated by repeated intravenous infusions of large amounts of fluid containing sodium bicarbonate and sodium chlorid. This resulted in increased urinary excretion and particularly in the excretion of large amounts of acetone bodies. In the study of these cases it was noted that by this therapy the ketosis in many cases was alleviated, often for several days, and that the cases which showed greatest improvement were those in which there was the largest excretion of acetone bodies.

(b) On the other hand, after the advent of insulin, it became the custom to treat cases of diabetic ketosis with frequently repeated doses of insulin and glucose, together with moderate amounts of fluid by mouth or by hypodermoclysis. On analysis of this group of cases, particularly those who eventually died, it was found that there were several who on this régime failed rapidly during the first twenty-four hours after admission, with symptoms of circulatory collapse, and with the kidneys either excreting no urine at all, or else excreting urine which contained only traces of acetone bodies.

(c) In still another group, it was found that a rapidly failing course, such as described in (b) above, was often suddenly and strikingly remedied by repeated intravenous infusions, with a coincident recovery of renal efficiency and flushing out of acetone bodies in large quantities.

In this study it was seen that patients in severe diabetic ketosis might recover without insulin. On the other hand, some of those treated with insulin died of renal insufficiency. A phase of renal insufficiency that frequently puzzled was the state of ketosis without ketonuria. A factor of importance in overcoming renal insufficiency was the production of diuresis, achieved best by the use of intravenous fluids.

Relief from Ketosis Without the Use of Insulin. Previous to 1923 many patients in ketosis were temporarily relieved by infusions, only to sink deeper into coma and die of diabetes. This is demonstrated by a typical case, No. 54705.

CASE NO. 54705.—The patient, a housewife, aged forty-four years, had been treated for diabetes for three years. She had been drowsy for one month with some improvement from time to time. On examination she was very restless; pulse was 150, and there was acetone odor to breath. Blood sugar was 5 gm. per liter; blood CO_2 -combining power was 12 volumes per cent; urine ferric chlorid test, 3+; sugar, 4+. Following intravenous

infusion of sodium bicarbonate, she became quiet and comfortable and said she felt well. Pulse dropped to 106. The improvement was only temporary and in spite of fluid forced by all routes she sank deeper into coma and died, forty-eight hours after admission. Autopsy showed nothing striking.

This illustrates what happened to a great many cases of diabetic coma before insulin, with temporary response following infusions, and subsequently steadily downhill course.

Two young diabetics demonstrated the fact that recovery from severe ketosis may take place without insulin, following a marked diuresis of acetone bodies. They are numbers 51477 and 48015.

CASE No. 51477.—The patient, a girl, aged twelve years, was admitted with a two-year history of diabetes. One year previous she had had a short period of drowsiness. The night before entering the hospital she neglected her diet and became drowsy. On admission she could be aroused, was semicomatose, hyperpneic, with strong acetone breath. Her blood CO_2 -combining power was 13 volumes per cent. Urine: ferric chlorid test, 4+; glucose, 4+. During the first two days she received 40 per cent of her body weight in fluids, with large amounts of alkali and glucose, comprising three intravenous infusions in all; 3150 cc. by vein, 4550 cc. by mouth, containing 81 gm. of sodium chlorid and sodium bicarbonate. She voided 2600 cc. with 4+ ferric chlorid test. The second day she received 6000 cc. of fluid and voided 4500 cc. with 4+ ferric chlorid test. Blood CO_2 -combining power rose to 24 volumes per cent and she became bright and comfortable for a week, when she again developed symptoms of ketosis while on a diet. Again, following intravenous infusions, she became comfortable. The patient left the hospital against advice three weeks after admission, improved.

CASE No. 48015.—The patient, a girl, aged nine years, had had symptoms of diabetes for only ten days. Three days previous to admission she began vomiting, became drowsy and stuporous. On examination she was found to be drowsy, but could be aroused. Breathing was deep, and acetone odor was noticed. Urinalysis: ferric chlorid test, 4+; glucose, 4+; blood sugar, 3.8 gm. per liter; blood CO_2 -combining power, 10 volumes per cent; blood acetone, 1.1 gm. per liter. The patient was treated by forcing fluids and was given sodium bicarbonate and carbohydrate. She voided large amounts, containing over 20 gm. of acetone in twenty-four hours, and responded rapidly, being discharged after three weeks in the hospital, in good condition. The patient has lived a normal life for ten years, on diet and insulin, entering college, September, 1929.

Renal Insufficiency. Disturbances of kidney function have been frequently encountered in ketosis, in those treated with, as well as in those treated without insulin. Most of our patients while in ketosis showed albuminuria, cylindruria, and often an elevation of the blood urea. Many of those who recovered had been critically ill. In these instances the severe symptoms seemed associated with falling blood pressure. Oliguria and anuria often followed a paroxysm of vomiting. Two patients who demonstrated the sequence of events following a disturbance of renal function were numbers 65330 and 56481.

CASE No. 65330 (Chart I).—The patient, an American school boy, aged sixteen years, had been living on a diet and insulin for three years. Following an upper respiratory infection three days before admission, he became ill. Twenty-four hours before entering the hospital he stopped

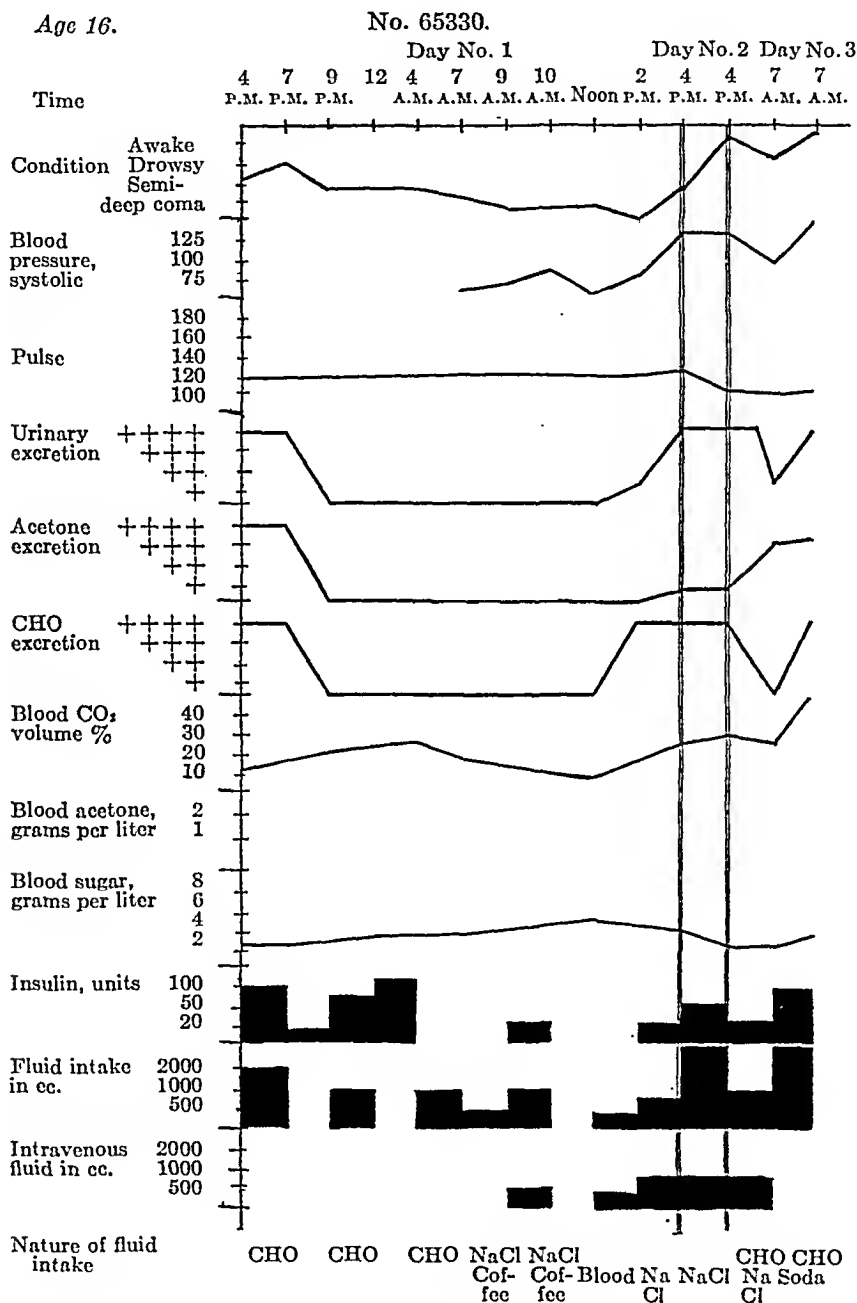


CHART I.

taking insulin, became drowsy and suffered difficulty in vision and epigastric pain. On admission, he was drowsy, pale and dehydrated, with Kussmaul breathing. Pulse rate was 120, excellent in quality. There was acetone odor and bilateral ptosis. Urine: ferric chlorid test, 4+; glucose, 4+; blood CO₂-combining power was 14 volumes per cent; blood

sugar, 3.45 gm. per liter. The patient was treated with 100 units of insulin, 2000 cc. of fluids enterally and subcutaneously, 150 gm. of carbohydrate and heat. Symptoms subsided. Three hours later, following a period of vomiting, he again became drowsy and noticed visual disturbances. Blood CO_2 -combining power rose slowly to 20 volumes per cent. During the night the patient was given 200 units of insulin and 200 gm. of glucose by hypodermoclysis, receiving 2500 cc. of fluids subcutaneously. Vomiting and restlessness continued and the patient became worse. Voiding stopped in the early part of the evening, and in the morning the patient could not be aroused. Pulse became weak and blood pressure was found to be 70 systolic and 40 diastolic. Following an infusion of saline solution blood pressure rose to 84 systolic and 50 diastolic. Anuria persisted and the patient remained semicomatose. Two hours later the patient was found to be completely comatose and the radial pulse could not be felt. A half hour after a transfusion of 300 cc. the blood pressure rose to 90 systolic and 60 diastolic, and 120 cc. of urine were obtained on catheterization. An hour later the patient began to void spontaneously and became rational. Improvement was steady for twenty-four hours, when the patient again became restless, complaining of visual disturbances and vomiting. Urine was found to be sugar free, although blood sugar was 3.1 gm. per liter, later 3.4 gm. per liter. Blood pressure and blood CO_2 -combining power fell. Following an intravenous infusion of 1000 cc. of saline and glucose, the patient voided and symptoms disappeared.

It was of interest that the urine following anuria contained no acetone bodies, while the blood gave a nitroprussid reaction for acetone bodies. During a period of oliguria on the third day in the hospital the blood sugar was markedly elevated and the urine gave a negative reaction to Fehling solution and Benedict solution.

CASE NO. 56481.—The patient, a girl, aged twenty-one years, was admitted, for the sixth time, in profound coma of over six hours' duration, with blood CO_2 -combining power of 10 volumes per cent and blood pressure of 75 systolic and 40 diastolic. She had been drowsy for several days and omitted insulin for twenty-four hours because of nausea and vomiting. The sequence of events was as follows: 4 to 7 A.M.: No response from hypodermoclysis of glucose and 100 units of insulin. Indwelling catheter was inserted. 7 to 8 A.M.: Coma less deep following intravenous infusions of 1000 cc. of 5 per cent glucose, with insulin, 50 units, and sodium bicarbonate, 20 gm. Hypernea unchanged. Blood CO_2 -combining power rose only to 14 volumes per cent. 8 A.M. to 2 P.M.: Acetone disappeared from urine at 9 A.M., and then all voiding ceased. Condition fluctuated—patient maniacal at times, deeply comatose and occasionally able to answer questions; no improvement. 2 to 4 P.M.: Following infusion of saline, moderate amount of urine was excreted, 4+; ferric chlorid test. Hypernea was definitely less marked. Blood CO_2 -combining power rose to 24 volumes per cent. Patient was still very drowsy; slight improvement. 4 to 6 P.M.: Urine excretion stopped. Patient became more drowsy. 6 P.M.: Transfusion of 500 cc. of citrated blood. 7 P.M.: Blood pressure became higher than at any time since admission, urine began to be excreted, acetone present in considerable quantity, progressive improvement clinically.

It was of interest that two out of three infusions were followed by diuresis of short duration, that transfusion was followed by normal voiding, that failure to excrete acetone bodies appeared to be the harbinger of renal shutdown and that large quantities of albumin were excreted during ketosis. It was puzzling that this patient, who voided on admission and 450 cc. a few hours later, stopped excreting urine under treatment.

The first patient represented ketosis following infection with usual treatment and improvement. Circulatory renal collapse, followed by an exacerbation of symptoms, resulted in what was almost a fatal termination. Excretion of urine began, following the elevation of blood pressure after transfusion on the second day in the hospital and following an infusion on the third day in the hospital. The fall of blood pressure on each occasion came shortly after a severe period of vomiting.

The second patient demonstrated that in diabetic ketosis there may occur a disturbance of renal function, in this case characterized by a failure to excrete acetone, followed by anuria, and accompanied by falling blood pressure and aggravation of symptoms. Treatment for diabetes was of no apparent help and it was only after the elevation of blood pressure with intravenous fluids, particularly by blood transfusion, that renal function was restored and recovery took place.

Death occurred, following renal shutdown, in 16 of our patients (18 per cent) treated with insulin. These presented the appearance of circulatory renal collapse comparable to some poisonings or surgical shock, with low blood pressure and anuria. This occurred both in young and elderly patients while the underlying condition of ketosis was being attacked with carbohydrate, insulin, and fluids. The failure of the kidneys to excrete and the retention of acetone bodies formed a vicious circle resulting in death unless renal function was reestablished, irrespective of the amount of carbohydrate burned with insulin. In those patients who were autopsied nothing abnormal was found in the kidneys. Typical examples of this downhill course were:

CASE No. 66033.—The patient, a girl, aged fourteen years, had diabetes for over a year, living on a diet with insulin, 15-0-15. Four days before insulin was stopped, and thirty-six hours before she began to vomit. She had been drowsy for twenty-four hours and in coma at least sixteen hours before admission. During that period she had received 125 units of insulin without any improvement.

Examination revealed a girl in deep coma. Her blood pressure could not be read, although a slight oscillation of the mercury column appeared at 40 mm. Bladder was empty on catheterization. Blood sugar was 3.7 gm. per liter. In the hospital she was given intravenously an infusion of 1000 cc. of 10 per cent glucose and 100 cc. of 5 per cent sodium bicarbonate. Blood pressure rose to 118 systolic and 54 diastolic. She voided once—sugar, 4+; ferric chlorid test, 2+; but in spite of insulin, carbohydrates, saline, soda, stimulants and fluids by vein, she died in twelve hours, being anuric except for a short time following the infusion.

CASE No. 64160.—The patient, a woman, aged thirty-six years, was known to have diabetes, but did not maintain her diet. Two days before admission she complained of drowsiness and epigastric pain. She had been in coma for twenty-four hours before admission and anuric during that period. Only 150 cc. of fluid were found in the bladder, which had collected for over twenty-four hours. In spite of intravenous glucose and saline in

large amounts she did not void. Insulin was given as well as stimulants. Blood pressure was 42 systolic. During twelve hours she received 410 units of insulin, 150 gm. of glucose, 30 gm. of sodium bicarbonate and 4500 cc. of fluid by all routes. In this period only 200 cc. of urine were obtained, which was probably a residuum in the bladder. She became steadily worse and died twelve hours after admission.

In both of these patients renal excretion was absent, and with the loss of that channel for the removal of acetone bodies, the oxidation of carbohydrate with insulin was not of apparent value.

Ketosis Without Ketonuria. Inasmuch as ketonuria is a common criterion of ketosis the absence of a ferric chlorid or nitroprussid reaction in the urine of a patient in diabetic coma, especially with a normal blood CO_2 -combining power, following the administration of sodium bicarbonate, may be confusing. This condition, ketosis without ketonuria, which has been observed and reported in other clinics, occurred in 6 (16 per cent) of our patients before 1923 and in 15 (16 per cent) of those treated with insulin. All of the former died, while all of the latter presented difficult problems. Of these, 5 died without resumption of acetone excretion; 9 remained drowsy until the kidneys excreted ketones, and 1 patient with a moderate ketonemia recovered without a resumption of excretion of acetone bodies. In 3 patients with indwelling catheters, it was seen that the disappearance of acetone from the urine preceded anuria. The following patients demonstrated the sequence of events that occurred in this condition of ketosis without ketonuria.

CASE No. 61852.—The patient, a colored girl, aged twelve years, had been treated at the hospital with diabetes for four years, having been in ketosis on three previous occasions. On each of these she had excreted ketones, 4+, and glucose, 4+, in her urine, and made a good recovery. She was on a diet of 130-65-140,* with insulin 25-0-15, when, following an upper respiratory infection, she became drowsy thirty-six hours before admission. On examination she was comatose; blood pressure was 120 systolic and 80 diastolic; urine showed sugar 4+ and ferric chlorid test 1+. Blood CO_2 -combining power was 14 volumes per cent and blood sugar was 4 gm. per liter. During the first few hours she was treated with insulin; hypodermoclysis of saline, stomach lavage with instillation of sodium bicarbonate, urinary bladder catheterization and glucose and sodium bicarbonate by rectum. After having received insulin, 175 units; carbohydrate, 155 gm.; sodium bicarbonate, 10 gm.; fluid, 1600 cc., and sodium chlorid, 5 gm., coma became deeper. She was given an infusion of 200 cc. of 10 per cent glucose and digitalis hypodermically. Death occurred a few hours later. Necropsy showed nothing significant. The kidneys appeared normal. On the previous admissions she had excreted large amounts of acetone bodies and recovered, but in this final period of coma urine contained only slight trace of acetone, although ketosis was marked. Following the use of insulin, carbohydrate and fluid, she sank into deep coma and died within twelve hours.

* These figures here and subsequently refer to grams of carbohydrate, protein and fat respectively.

CASE No. 69774. The patient, a boy, aged seven years, known to have diabetes for three years, was admitted with a twenty-hour history of ketosis, accompanied by vomiting. He appeared hyperpneic and rather pale, yet was able to answer questions satisfactorily. Urinalysis revealed glucose 4+ and ferric chlorid test 4+. The blood sugar was 6.9 gm. per liter and the CO₂-combining power was only 12.8 volumes per cent. Eight hours later, following insulin, 70 units, glucose, 125 gm., sodium chlorid, 4.5 gm., sodium bicarbonate, 5 gm., and fluid, 2000 cc., enterally and subcutaneously, the blood sugar was 1.1 gm. per liter, and the CO₂-combining power was 40.4 volumes per cent, while the urine showed glucose 4+, ferric chlorid 1+ and nitroprussid test 2+. The patient's condition had become quite different; hyperpnea and pallor were followed by drowsiness and oliguria. Following an intravenous infusion of 700 cc. of 10 per cent glucose with 40 units of insulin, he voided large quantities (glucose, 4+; ferric chlorid test, 0). Eight hours later his blood sugar was 3.45 gm. per liter and blood CO₂-combining power was 49 volumes per cent. In spite of the rising blood CO₂-combining power, he appeared comatose, aroused occasionally only to cry. Neurologic signs, including a positive Kernig sign and stiff neck, suggested the possibility of a concomitant, central nervous system disease. Six hours later, without any treatment, he suddenly began to excrete ketones in large quantity (ferric chlorid test, 4+); simultaneously his stupor and neurologic signs disappeared.

This patient was drowsy, with an almost normal blood CO₂-combining power. Although the urine was free of acetone bodies, he was in ketosis, which did not clear up with the oxidation of carbohydrate. The excretion of acetone bodies was followed by rapid disappearance of symptoms.

CASE No. 69797.—The patient, a woman, aged twenty years, was admitted for the second time in ketosis. She was taking 65 units of insulin a day, but not adhering to a diet. Following a furuncle on her lip four days previous she began vomiting. On admission she was able to answer questions and was quite restless and dyspneic. Blood CO₂-combining power was 20 volumes per cent. Urine gave a 4+ ferric chlorid reaction and contained 5 per cent sugar. Blood pressure was 110 systolic and 60 diastolic. Following the initial infusion, the patient voided a large quantity of ketones (2.59 or 3.4 gm. per liter). During the next twelve hours, while taking 25 units of insulin each hour, adequate glucose by mouth and 1500 cc. of normal saline subcutaneously, urination ceased and her blood CO₂-combining power, which rose to 30 volumes per cent accompanied by disappearance of hyperpnea, fell to 22 volumes per cent, with the patient becoming irritable. After a second infusion the patient again voided, but only small amounts of acetone (0.096 or 0.13 gm. per liter). This specimen had a 1+ nitroprussid test and a negative ferric chlorid test. Six hours later the urine had a negative test for acetone bodies and the blood CO₂-combining power was only 22 volumes per cent. Quantitative acetone of blood done at this time showed 0.43 gm. per liter. Twelve hours later, when on a similar régime with less insulin, she voided urine with 2+ ferric chlorid and 3+ nitroprussid tests (0.6 gm. per liter). Improvement was marked and continued. Flushing the kidneys on admission removed a large quantity of ketones, and then, while under treatment, disturbances of renal function occurred. An intravenous infusion similar to the one given twelve hours before was followed by diuresis without acetone bodies. These were retained, as shown by the blood findings and the subsequent flushing of ketones.

CASE No. 64399.—The patient, a Jewish girl, aged twenty years, was admitted for the second time, having had diabetes for three years, living

on a diet of 250-80-80 with insulin. For twenty-four hours before admission she had had abdominal pain, nausea and vomiting, and became semi-comatose nine hours previous to entering the hospital. On examination she was restless, uncomfortable and nauseated, with a pulse of 128 and a blood pressure of 90 systolic and 50 diastolic. Urine showed glucose 4+, but the ferric chlorid reaction was 0. Blood CO_2 -combining power was 15 volumes per cent. Treatment consisted of insulin, glucose and alkalis. On admission the blood pressure was 90 systolic and 60 diastolic, the blood CO_2 -combining power was 15 volumes per cent and the ferric chlorid reaction was 0. Following an infusion of 500 cc. of normal saline and glucose, with insulin, 75 units, she excreted considerable urine showing ferric chlorid reaction of 2+. Another infusion containing sodium bicarbonate was followed by similar urine excretion. The blood pressure rose, and the blood CO_2 -combining power became 40 volumes per cent. The next day, while the CO_2 -combining power was 65 volumes per cent, the blood pressure fell to 92 systolic and 67 diastolic. The urine gave a negative ferric chlorid reaction and the patient seemed irritable and nauseated. She was given 50 units of insulin, 1500 cc. of fluid and glucose enterally and subcutaneously. The day following she was worse. The blood CO_2 -combining power fell to 25 volumes per cent. She was nauseated and vomiting. The urine still gave a negative ferric chlorid reaction. An intravenous infusion of 700 cc. of normal saline, glucose and insulin was followed by diuresis; urine giving ferric chlorid reaction of 4+. A similar infusion was followed by the excretion of 700 cc. of urine; ferric chlorid reaction, 4+. After this the pulse fell from 128 to 80 and symptoms disappeared. The patient volunteered the information that she then felt normal for the first time since admission.

This patient, while under treatment for three days, excreted acetone bodies in small amounts with a ferric chlorid reaction of 0 or 2+. She remained uncomfortable, nauseated and continued to have a low blood pressure. It was not until the third day that, following intravenous infusion, she suddenly excreted large amounts of acetone and simultaneously became symptom free.

CASE No. 71851.—The patient, a boy, aged eleven years, was admitted with a three-week history suggesting diabetes. On examination he was found to be in good condition, but the blood CO_2 -combining power was only 15 volumes per cent and the blood sugar was 2.5 gm. per liter. He was placed on a diet with insulin and seemed to be progressing satisfactorily, when twenty-four hours after admission he began vomiting a great deal and grew drowsy. Pulse became poor and blood pressure was found to be only 75 systolic and 50 diastolic. Although the blood CO_2 -combining power had risen from 14 to 31 volumes per cent with insulin and carbohydrate, the urine, which had contained large amounts of acetone, ferric chlorid reaction 4+, acetone 9.38 gm. per liter, at this time showed ferric chlorid test 2+, acetone 2.33 gm. per liter. The blood acetone was 0.114 gm. per liter. The patient, following intravenous infusions of saline and glucose with insulin, passed large quantities of urine, but the ferric chlorid reaction became negative (acetone, 0.122 gm. per liter). For twelve hours the patient was difficult to arouse, pulse remained poor and blood pressure low. Although the urine continued to show ferric chlorid test 0, the blood-acetone content diminished from 0.114 gm. per liter to 0.052, then 0.0322 and then 0.0198, with a blood CO_2 -combining power of 29 volumes per cent. Recovery was slow; the acetone bodies were cared for by the oxidation of carbohydrate with insulin.

These patients in ketosis appeared to retain acetone bodies in their tissues without excreting them in the urine. Some of them recovered promptly, following the flushing of acetone bodies. One third of these patients sank rapidly into coma, became anuric, and died. All of them presented difficult problems. There was only one recovery without a resumption of acetone excretion by the kidneys.

The Importance of Diuresis. In patients who passed but small amounts of urine, the disappearance of the symptoms of diabetic coma was usually slow. In the patients who excreted no acetone bodies, the outcome was often fatal, and in those who became anuric, death nearly always followed. In contrast to these patients, typical protocols of which have already been given, there were others who recovered satisfactorily. Among the latter the rapidity of change from coma to health appeared directly in proportion to the diuresis of acetone bodies. Characteristic cases demonstrating the effect of diuresis are:

CASE NO. 76234.—The patient, a school girl, aged twelve years, had been treated for diabetes for four years. For the past two years she had been on a diet of 60-60-90 with insulin, 14 units a day. She had been spilling a little sugar for a few days previous to admission. Twenty-four hours before admission she began vomiting. This continued. There was no obvious explanation for the precipitation of ketosis. On admission she was found to be extremely restless and uncomfortable. Blood sugar was 7.38 gm. per liter; CO_2 -combining power was 12 volumes per cent; blood pressure was 120 systolic and 60 diastolic; urine sugar was 5 per cent and ferric chlorid reaction was 4+. She was given 20 units of insulin and an intravenous infusion of 1100 cc. of 5 per cent glucose. This was followed by small amounts of insulin and an intravenous infusion of 500 cc. containing 50 gm. of glucose, 12 gm. of sodium bicarbonate and 5 gm. of sodium chlorid. Following the first infusion, the patient voided 1100 cc. in two hours, containing acetone, 4.97 gm. In the next four hours she voided 300 cc., containing acetone, 1.1 gm. Following second infusion, she voided 200 cc. in six hours with acetone, 0.51 gm. Following two infusions, the patient practically freed herself in eight hours of ketones, voiding approximately 1600 cc., containing acetone, 6.58 gm.

This patient, having had 50 units of insulin, made a rapid response in three hours of treatment from severe ketosis to comfort, following diuresis and excretion of large amounts of acetone bodies.

CASE NO. 63959.—The patient, a girl, aged sixteen years, was known to have diabetes for three years and had been on a diet of 100-65-100 with insulin, 25-0-10. For twenty-four hours she had been irritable and complained of pain in the abdomen. Two hours before admission she became comatose and vomited a great deal. The cause of this break was probably an upper respiratory infection. On admission, CO_2 -combining power was found to be 5 volumes per cent, blood sugar was 8.6 gm. per liter, urine ferric chlorid reaction 4+ and sugar 4+. She was treated with small doses of insulin every hour, intravenous infusions and so forth, and made an excellent response. During the first intravenous infusion, after having received 500 cc. of glucose, she came out of coma and recognized those at her bedside. At the end of the intravenous infusion (2000 cc. of 5 per cent

glucose, saline, with 20 gm. of sodium bicarbonate) she was much improved. During this period of one and a half hours she voided 1050 cc. It was thought that she came out of coma after flushing a large quantity of acetone (3.7 gm.) and then improved steadily with glucose, frequent small doses of insulin and fluid.

The Necessity of Intravenous Fluids for Diuresis. To obtain rapid diuresis the administration of insulin, carbohydrate, alkalis, fluids and stimulants was not found to be sufficient. Patients in diabetic coma or severe ketosis commonly presented a picture similar to surgical shock with a falling blood pressure and circulatory renal collapse. In these cases, fluids administered by hypodermoclysis or to the gastrointestinal tract were absorbed slowly, or not at all, and renal function ceased following a fall in blood pressure. In contrast, those measures which have proven themselves of service in overcoming surgical shock were of most help in severe ketosis. Blood transfusions proved the best agent for maintaining blood pressure; the slow intravenous infusion of large amounts of hypertonic fluids containing glucose and alkali was of great value in overcoming circulatory renal collapse and causing diuresis. The following are typical examples, demonstrating the necessity of intravenous fluids:

CASE No. 56381.—The patient, a girl, aged twelve years, was admitted for the second time with a five-year history of diabetes and increasing drowsiness of twelve hours' duration. She was on a weighed diet of 130-60-100 with 48 units of insulin before breakfast. Dietary indiscretion was probably responsible for the onset of her break. Blood sugar was 3.45 gm. per liter, CO₂-combining power was 10 volumes per cent, urine sugar was 4+, ferric chlorid reaction was 4+ and blood pressure was 50 systolic and 30 diastolic.

After receiving during the first six hours 45 units of insulin, hypodermoclysis, fluids by mouth and by rectum and sodium bicarbonate, the patient had a rise in CO₂-combining power from 10 to 26 volumes per cent and vomited, becoming more drowsy; ferric chlorid reaction, which was 4+ on admission, became 0; blood pressure fell to 50 systolic and 30 diastolic; anuria followed. At 8 A.M. she sank into coma and was then given infusion of 1000 cc. of 5 per cent glucose. Following this, the blood pressure rose; the pulse fell in a few hours from over 180 to 100; the excretion of urine began (ferric chlorid reaction, 2+) and symptoms disappeared gradually. The urine contained more and more acetone; ferric chlorid test later, 3+ and 2+.

This patient received insulin, fluids, glucose and sodium bicarbonate without any intravenous treatment. The blood pressure remained low. The patient did not excrete urine following the initial admission specimen, and sank into coma. Following an infusion of glucose, the blood pressure rose. She again voided. Ferric chlorid reaction became more strongly positive and the clinical picture became satisfactory.

CASE No. 62184 (Chart II).—The patient, a school girl, aged fifteen years, was known to have diabetes for three years. She was discharged from the hospital three years previous on a diet without insulin and later was placed on a diet of 250-75-75, with insulin 40-0-20. Seven hours

before admission she complained of abdominal pain and nausea, vomited and became drowsy. She was given 40 units of insulin. There was no definite evidence to explain the break. Examination revealed an extremely drowsy girl, difficult to arouse, with marked expiratory grunt. Blood

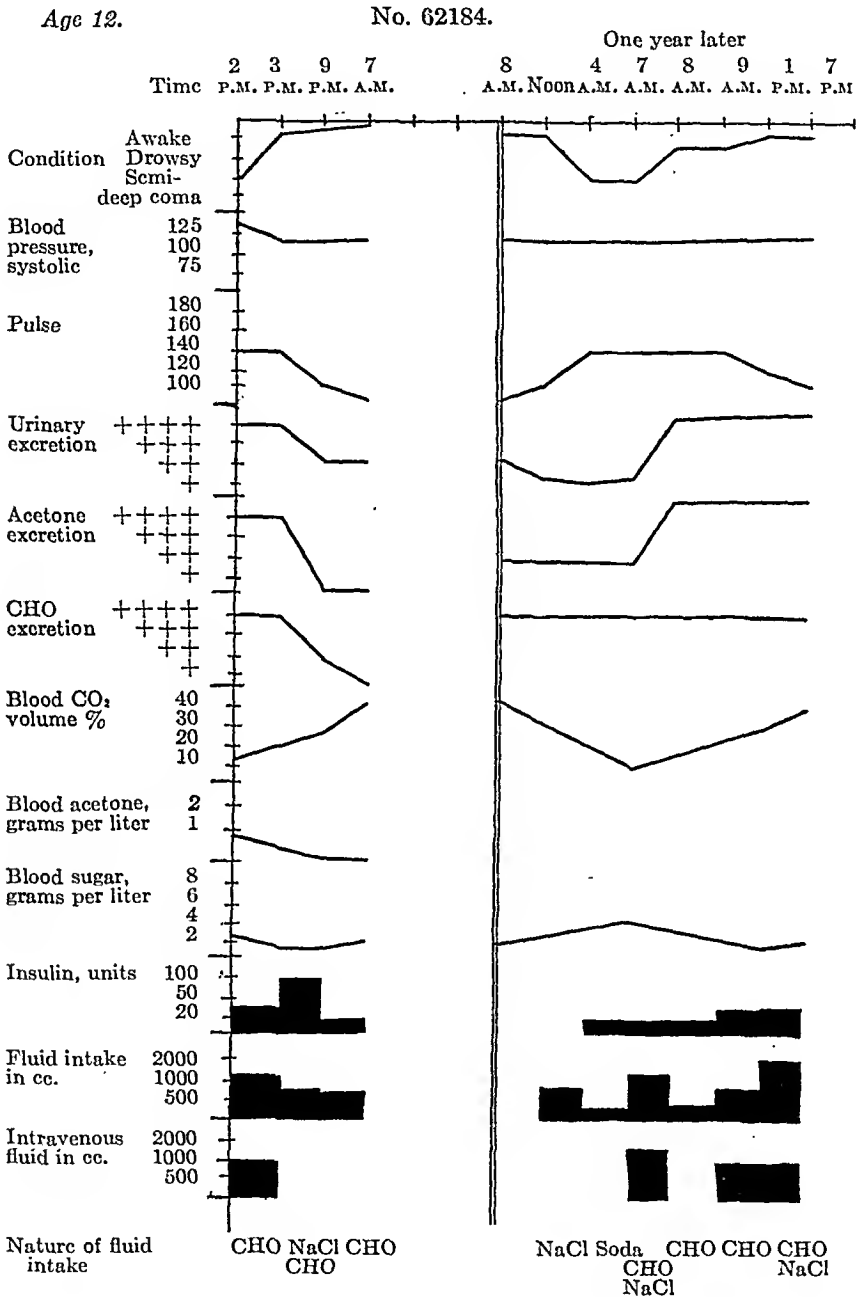


CHART II.

CO₂-combining power was 16 volumes per cent, blood sugar was 2.59 gm. per liter, urine sugar was 4+ and ferric chlorid reaction was 4+. On admission she was given glucose by intravenous infusion and saline solution by hypodermoclysis, with a moderate amount of insulin. Her blood pressure remained normal. A striking change took place immediately after the

intravenous infusion (1000 cc. of 10 per cent glucose with 50 units of insulin). She volunteered the information that the pain had gone and recognized those at the bedside; skin became warm and cyanosis disappeared. Within an hour she voided 550 cc. Hyperpnea persisted for three hours. When infusion was given on admission blood acetone was 0.75 gm. per liter. About one hour after infusion patient voided 550 cc.; ferric chlorid reaction, 4+. Four hours later blood acetone was 0.25 gm. per liter and blood CO_2 -combining power was 28.4 volumes per cent. Urine ferric chlorid reaction was negative after the first diuresis. Twelve hours later blood acetone was almost absent.

Clinically it seemed that rapid changes followed the diuresis of ketones.

The same patient was readmitted the next year. On a similar diet she now required 50 units of insulin, when previously she had taken 110. There was a spilling of a small amount of sugar. Two days before she became nauseated and vomited. There was no evidence that explained precipitation of ketosis. She was admitted in fairly good condition to have her diet regulated. Her blood pressure was 120 systolic and 100 diastolic, blood sugar was 1.02 gm. per liter, blood CO_2 -combining power was 40 volumes per cent, urine sugar was 4+ and ferric chlorid reaction was 2+. She was given a hypodermoclysis of saline solution and water by mouth. Twelve hours later the patient was markedly restless and hyperpneic, with Kussmaul breathing and severe abdominal pain. Blood CO_2 -combining power had dropped from 40 to 12 volumes per cent. Condition became serious. Thus, after having a hypodermoclysis of 1000 cc. of saline and having had sodium bicarbonate, 10 gm., by mouth, with no vomiting, she slipped into semicoma. Following an intravenous infusion of 1500 cc. (saline and 5 per cent glucose) she voided 1050 cc., containing 4.5 gm. of acetone. Two more intravenous infusions and moderate doses of insulin were followed by the excretion of 0.76 and 0.36 gm. of acetone. After each diuresis the symptoms rapidly disappeared, that is, Kussmaul breathing, drowsiness, headache, pain in stomach and nausea.

This patient on two occasions responded clinically to diuresis. Fluids given by other route in the second instance were followed by development of ketosis. On the first admission she did well after an infusion. On the second admission she did poorly after hypodermoclysis, went into a coma and recovered quickly after intravenous infusion.

CASE No. 59106.—The patient, a girl, aged four and a half years, had been admitted one year before with diabetes had weathered a series of infections (diphtheria, measles, tonsillitis, Vincent's angina) and lived on a diet of 40–60–90 and insulin, 15–0–5. She contracted a cold a week before admission, began spilling sugar and was brought into the hospital to have her diet arranged. On admission she was quite well. Blood CO_2 -combining power was 30 volumes per cent and blood sugar was 3.7 gm. per liter. During her ten days in the hospital she continued to excrete acetone and glucose in large amounts. When diet was being changed and insulin was omitted for twelve hours she became markedly hyperpneic and was treated at once for impending coma, receiving in twenty-four hours a total of 220 units of insulin, 1200 cc. containing 120 gm. of glucose by hypodermoclysis, 300 cc. of glucose by rectum, 400 cc. of 5 per cent sodium bicarbonate by rectum and orange juice and sodium bicarbonate by mouth. She did not receive any fluid intravenously and vomited almost every hour, over fifteen times altogether. No urine was obtained with indwelling catheter. Anuria existed for twelve hours; pulse rose from 100 to 180. The blood CO_2 -combining power was 80 and 50 volumes percent, yet she died after one day of ketosis.

In this patient with a normal blood CO_2 -combining power, receiving

insulin, carbohydrates and fluid in large amounts, but none intravenously, the kidneys shut down and the patient died in ketosis.

CASE No. 224211.—The patient, a maid, aged nineteen years, was sent to the hospital as a case of poisoning, having been in deep coma for eight hours. She was not known to have diabetes mellitus; however, on catheterization her urine was found to contain glucose, 4+, and gave a ferric chlorid reaction of 1+. Examination revealed a pale girl in deep coma with extreme hyperpnea, tachycardia and marked odor of acetone to the breath. There was a cutaneous infection about the vagina. The blood pressure was systolic 138 and diastolic 90, the blood sugar was 5.16 gm. per liter, the blood CO₂-combining power was 13 volumes per cent and blood acetone was 1.21 gm. per liter.

The patient was given 40 units of insulin and 1000 cc. of 10 per cent glucose intravenously, followed by 1000 cc. of normal salt solution containing 20 gm. of soda. An indwelling catheter was inserted. During the infusion she excreted 1300 cc. of urine containing 5.56 gm. of acetone. Simultaneously she began to arouse. The blood acetone rose to 1.34 gm. per liter. Ten units of insulin were given every half hour and more intravenous fluids, consisting of 1000 cc. of 10 per cent glucose and 1000 cc. of saline. Following this infusion, she excreted 1900 cc. of urine, containing 10.37 gm. of acetone. During seven hours she changed from almost a moribund condition to a mental state which was nearly clear. During that time she voided 3200 cc., containing 15.93 gm. of acetone, although on admission her urine was nearly free of ketones. The blood acetone fell to 0.62 gm. per liter and the blood CO₂-combining power rose to 27 volumes per cent.

For twelve hours the patient was treated with glucose and orange juice by mouth, receiving 2660 cc., containing 80 gm. of glucose, and was given 10 units of insulin every hour. Although her blood pressure remained elevated and the blood CO₂-combining power had risen to 37 volumes per cent, the urine flow became scanty. It contained glucose, 4+ and gave only a 1+ ferric chlorid reaction. Vomiting began and the patient sank back into a semicomatose state. During intravenous infusions, consisting of 3000 cc. of saline and glucose, she excreted a large quantity of urine giving a 4+ ferric chlorid reaction. Simultaneously with her diuresis, she became mentally clear and subsequently made an uneventful recovery.

This patient made a prompt recovery from deep coma following infusions. The urine, which showed only a slight ferric chlorid reaction before the injection of fluids intravenously, contained large quantities of acetone during the diuresis. Subsequently, while taking adequate amounts of fluid and carbohydrate by mouth, with the necessary insulin, kidney excretion diminished, the urine showed again only a faintly positive ferric chlorid reaction, and the patient sank back into coma. Once more, following infusions, large quantities of acetone bodies were excreted and recovery was prompt.

These patients were examples that demonstrated the importance of administering fluids intravenously rather than by other routes.

Conclusion. 1. In the alleviation of acute ketosis urinary excretion of acetone bodies is of perhaps greater importance than their oxidation.

2. It has been repeatedly demonstrated in the group of patients presented that ketonemia may exist in absence of ketonuria. This condition appears at times to precede anuria and should be regarded as a warning to the physician.

3. The development of anuria greatly jeopardizes the recovery of a patient with severe ketosis.

4. Intravenous fluid has been of far greater value in causing excretion of ketone bodies and in correcting anuria than fluid administered by other routes.

5. Recovery from severe ketosis may depend largely upon the rapidity with which acetone bodies are excreted by the kidney, and may be prevented by the development of functional renal insufficiency.

REFERENCES.

1. Stadelmann, E.: Ueber die Ursachen der pathologischen Ammoniakausscheidung beim Diabetes Mellitus und des Coma Diabeticum, *Arch. f. exp. Pathol.*, 1883, 17, 443.
2. Von Frerichs, F. T.: Ueber den Diabetes, Berlin, August Hirschwald, 1884, p. 113.
3. Lepine, R.: Le diabète sucré, Paris, Alcan, 1909, p. 572.
4. Rosenbloom, J.: A Form of Diabetic Coma, *New York Med. J.*, 1915, 52, 294.
5. McCaskey, G. W.: Coma in a Fatal Case of Diabetes Without Diabetic or Beta-oxybutyric Acid, *J. Am. Med. Assn.*, 1916, 66, 350.
6. Feinblatt, H. M.: Report of a Fatal Case of Juvenile Diabetic Coma with Insignificant Ketonuria, and with a Large Amount of Acetone in the Spinal Fluid, *Arch. Int. Med.*, 1924, 32, 509.
7. Paddock, B. W.: A Fatal Case of Diabetic Coma Without Ketosis, *J. Am. Med. Assn.*, 1924, 82, 1855.
8. Starr, Paul; and Fitz, Reginald: Excretion of Organic Acids in the Urine of Patients with Diabetes Mellitus, *Arch. Int. Med.*, 1924, 33, 97.
9. Evans, G.: Diabetic Coma Without Ketonuria, *Lancet*, 1925, 1, 77.
10. Argy, W. P.: An Unusual Case of Hyperglycemia (1.71 per cent) with Coma; Associated with an Absence of Acetone in the Urine, *Boston Med. and Surg. J.*, 1925, 193, 1236.
11. Lemann, I. I.: Pitfalls in the Diagnosis of Diabetic Coma, *Med. Clin. North America*, 1926, 9, 959.
12. Lorant, I.: Coma Diabeticorum, *Klin. Wehnschr.*, 1926, 5, 216.
13. Oliver, T. H.: Diabetic Coma Without Acetonuria, *Lancet*, 1926, 1, 750.
14. Appel, K. E., and Cooper, D. A.: Diabetic Acidosis with Negative Ferric Chlorid Reaction in Urine, *Am. J. Med. Sci.*, 1927, 173, 201.
15. Rudy, A., and Levin, C. M.: Unusual Case of Diabetic Acidosis Without Ketonuria or Ketonemia, *New York State J. Med.*, 1927, 27, 1240.
16. Joslin, E. P.: The Treatment of Diabetes Mellitus, Lea & Febiger, 3d ed., p. 173.

THE PROBLEM OF PULMONARY TUBERCULOSIS IN PATIENTS WITH DIABETES.

BY REGINALD FITZ, M.D.

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.)

For many years it has been generally known that coma, vascular disease, including gangrene, and infections, including tuberculosis, have been the chief causes of death among patients with diabetes. Insulin has done much to do away with the dangers of coma. Almost every doctor at all interested in following up his diabetic cases has

several on record of recovered coma and it is not uncommon to meet individual diabetics who have been in deep coma on three or four occasions.

Gangrene, also, has been attacked with almost as striking results. While diabetic gangrene still causes many deaths, its immediate mortality is much less than in the pre-insulin days. Sensible preventive measures have been devised; patients are routinely taught, for example, to take the most punctilious care of even the slightest abrasion occurring on the hand or foot, and almost all have been warned that the loss of an arm or leg may be the penalty for needless glycosuria and a neglected scratch. Insulin certainly has done much to allow older diabetics to keep well and comfortable.

Infections are still dangerous. Of these, the acute self-limited infections like pneumonia or typhoid fever are far less of a menace to the diabetic on the whole than is such a chronic, insidious infection as tuberculosis. It is my purpose in this paper to review the clinical experience of the Medical Clinic of the Peter Bent Brigham Hospital, with pulmonary tuberculosis in diabetes, so as to awaken interest in behalf of the tuberculous diabetic, and to demonstrate that in diabetes, pulmonary tuberculosis is not a particularly rare complication and is often one of uttermost severity.

The Medical History of Tuberculosis in Diabetic Patients. Pulmonary tuberculosis has been recognized as a significant complication of diabetes for a long time. Probably Richard Morton¹ deserves credit for drawing attention to the importance of the subject by making the first case report in 1694. The matter has been discussed subsequently in a variety of ways. For instance, early in the nineteenth century the French investigators Nicolas and Gueudeville² were so impressed with the incidence of tuberculosis and diabetes as to write a monograph on "*la Phtisie Sucrée*," while a few years later in England, Copland and Bardsley³ stated that tuberculosis occurred so frequently in diabetes as to be a sign of this disease.

There have been published four theses from the University of Paris on the general subject of diabetes and tuberculosis. The first was in 1873 by Bertail,⁴ the second in 1888, by Bagou,⁵ the third in 1895, by Sauvage⁶ and the fourth in 1926, by Péronne.⁷ The time interval elapsing between these various publications is of interest, mirroring very fairly the changing fashions by which the various problems of diabetes have been approached. It was from 1870 to 1900 that the clinical aspects of diabetes appeared of greatest importance to the researcher. The method of clinical and pathologic correlation was generally employed and investigators were endeavoring to discover a definite pathology which might explain the complex clinical findings of diabetes.

From 1900 to the discovery of insulin there followed a period in which new laboratory methods were developed with great rapidity.

These were applied to the study of diabetes and resulted in explaining many of the chemical and physiologic reactions of this disorder. During these years, the strictly clinical aspects of diabetes appeared of relatively little interest, and clinical-pathologic studies on diabetes appeared less often.

The introduction of insulin in 1922, has reawakened, apparently, a new interest in the clinical phenomena of diabetes. Perhaps this depends on the fact that our diabetic patients are now living longer than they were and thus have greater opportunity to develop unusual complications, or perhaps Banting's discovery, emanating from a clinician, has stimulated other clinicians to investigate their cases more thoroughly. In any event, interesting and carefully written papers on various clinical or pathologic phases of diabetes are again appearing and are being published more frequently than they were a few years ago.

Recent literature on the subject of diabetes and tuberculosis is voluminous and very bewildering, especially in relation to the manner in which the tuberculous diabetic is affected by insulin. One can obtain all sorts of conflicting opinions. LeNoir and Scherrer⁸ have been able to divide roughly the recently published literature into three groups: there are authors who claim that even small doses of insulin may activate an inactive tuberculosis in a diabetic patient or may exaggerate the fever of a tuberculous diabetic and thus be injudicious to use; there are authors who believe that insulin has no particular effect on the course of tuberculosis in diabetes; and, finally, there are authors who believe that insulin can be definitely helpful in treating this particular combination of diseases.

If one were to make any general criticism of the already assembled literature, it would be that recent writers on diabetes and tuberculosis have tended to report but small groups of cases, followed for but short periods of time by any given method of treatment, and have failed to assemble any relatively large group of such cases carefully followed for a sufficiently long time to properly emphasize the life history of this combination of diseases.

The Seriousness of Diabetes and Tuberculosis. Wilder and Adams⁹ have been kind enough to send me the following statistical data from Rochester: Among the first thousand cases of diabetes studied at the Mayo Clinic after 1922, when insulin became available for general clinical use, there were 25 entering with gangrene, 29 entering with sufficient acidosis to produce a blood bicarbonate concentration of less than 25 volumes per cent and 10 entering with signs of active pulmonary tuberculosis. At the date of their letter, a little more than four years after the thousandth case was seen, and a little more than seven years after the first case was studied, 10 of the group with acidosis (34 per cent) are dead, 16 of the group with gangrene (64 per cent) and 7 (70 per cent) of the group with pulmonary tuberculosis. In other words, these figures suggest that in

any large group of diabetics, there will inevitably appear a certain number complicated by acidosis, gangrene and pulmonary tuberculosis. If the cases are followed for a sufficiently long period of time after they are first observed, it will become evident that an attack of diabetic acidosis has no profound effect on a patient's life expectancy. A patient who has gangrene may escape death during the immediate attack but is unlikely to live for many years thereafter. A patient who is unfortunate enough to contract pulmonary tuberculosis will probably succumb to his combination of diseases with disheartening rapidity. Of these three major complications of diabetes, infection in the form of pulmonary tuberculosis is, at present, by all odds the most serious.

The Incidence of Pulmonary Tuberculosis in Diabetes. In the Peter Bent Brigham Hospital and its Outdoor Department from October 1, 1922, to January 1, 1929, there appeared 1529 patients with diabetes, and of these 35 had or developed subsequently active pulmonary tuberculosis. Joslin¹⁰ reports 43 cases among his last published 3000 cases. Combining the figures of Wilder and Adams with these, it appears that in a group of more than 5500 diabetics the incidence of pulmonary tuberculosis was approximately 1.6 per cent. Admitting that there are upward of a million diabetics in the country alive today, there must be approximately 16,000 with tuberculosis to be taken care of, a sufficiently impressive number to demand serious consideration.

It has been suggested that all patients with diabetes are particularly prone to develop pulmonary tuberculosis, and this may be true. Joslin has reported the age incidence at time of onset of 2611 cases of diabetes observed in his clinic, and Adams,¹¹ similar data from 1000 cases in the Mayo Clinic. Diabetes develops in people of all ages from infancy onward, but is found most frequently in adults at about the age of fifty years. Tuberculosis, too, develops in people of all ages. The age incidence of active tuberculosis in the Peter Bent Brigham Hospital group of diabetic patients is not unlike the age incidence of diabetes in the combined series of Joslin and Adams. Tuberculosis, fortunately, is not often encountered in young diabetics and tends to be seen more often in the elderly ones. On the whole, however, one gets the impression that tuberculosis develops most easily where it has the best opportunity; it is relatively uncommon in young diabetics because diabetes is a relatively rare disease in youth and more common among older diabetics because there are so many more of them in existence to have a chance to become infected.

The Cause of Tuberculosis in Diabetes. There are perhaps many reasons why a person afflicted with a wasting disease like diabetes might acquire tuberculosis. The records of the Brigham Hospital cases have been analyzed in an attempt to discover some specific reasons why our particular cases should have picked up the com-

plicating infection. No definite conclusions can be drawn but one gathers some interesting impressions.

In the 3000 cases reported by Joslin there were 43 cases of tuberculosis or about 14 in each thousand. Wilder and Adams saw 10 cases of tuberculosis in 1000 cases. In our series of 1529 diabetics were 35 cases of tuberculosis or about 23 per thousand. Evidently we have met with a higher proportion of tuberculous cases than have Joslin or the Mayo Clinic. In all probability this discrepancy depends on differences in social conditions of the various groups of cases. The Peter Bent Brigham Hospital cares largely for the poor of Suffolk County in Massachusetts, while Joslin and the Mayo Clinic draw patients from all over the world and do not deal so exclusively with people of straitened means. It appears that the needy diabetic is the most liable to develop tuberculosis and on this account requires especial assistance.

In most of our cases the diabetes was known to exist for some time previous to the development of the pulmonary tuberculosis, although in several, both diseases were first recognized at the same time. In a few cases, as judged by Roentgen ray, there was an old tuberculosis which flared up as a late complication of diabetes. In general, therefore, the tuberculosis of diabetics is an acute fresh process and but seldom is grafted on an old quiescent infection.

The occupations of our group varied very widely but one striking fact is that 74 per cent were employed in some form of indoor sedentary work. Properly supervised exercise is now recognized as an important adjunct to good diabetic therapy, and perhaps may even help to serve as one of the means of preventing the development of tuberculosis in diabetes.

The family histories of our cases are of some interest. Eleven of the group (31 per cent) had tuberculosis in their families and 5 (14 per cent) diabetes. Two cases (6 per cent) had a family history of both diabetes and tuberculosis. In 17 cases (49 per cent), however, there was no known history of either diabetes or tuberculosis. Thus direct contact or a familial tendency to either diabetes or tuberculosis did not appear of striking importance.

Most of our patients at one time were obese, and rapid loss of weight appeared to be the most constant single factor through which both diseases became recognized. On the whole, a stout rather elderly person, in poor circumstances, possibly with a family history of either diabetes or tuberculosis, leading a sedentary indoor life without exercise and developing diabetes which was untreated and accompanied by a rapid loss of weight, appeared to be the most likely candidate to succumb to a complicating tuberculosis.

The Importance of Adequate Treatment in Diabetes. Our cases fall into two distinct groups: there were 11 cases (30 per cent) which developed tuberculosis while under treatment for diabetes and 24 (70 per cent) which were discovered to have active tuberculosis at

the time they were first seen in the Brigham Hospital Clinic. The fact that so large a proportion of the cases developed tuberculosis while under observation is of course very striking and deserves special comment.

Carelessness in treatment plays havoc with a diabetic. Most of our cases which developed tuberculosis while under observation did so through lack of properly supervised treatment. It is difficult to formulate any definite description of an ideal treatment for diabetes and even more difficult to carry out anything approaching an ideal treatment in outpatient work. It is apparent, however, that any doctor or clinic undertaking to care for diabetic patients must employ some system of follow-up work by which the patients are examined systematically at frequent intervals and are kept track of for long periods of time. The case which does not improve must be suspected of having tuberculosis. Every diabetic patient owes himself repeated examinations each year as well as routine blood-sugar determinations and urinalyses.

The Diagnosis of Pulmonary Tuberculosis in Diabetes. It was formerly my impression that pulmonary tuberculosis may be difficult to recognize in diabetic patients. Yet a careful review of the records of the Peter Bent Brigham Hospital cases does not bear out this impression. For several years we have had Roentgen ray films made of the chests of almost every diabetic patient that came to the hospital. In 1927, Sosman and Steidl¹² reviewed the radiologic findings of 17 of our cases and found that hilum infiltration was evident in every instance. In the early stages, on this account, tuberculosis may be difficult to recognize clinically.

If one goes over our clinical records from the viewpoint of physical signs, however, it appears that regardless of how the process began, most of the cases developed in a short time the common physical signs of pulmonary tuberculosis with dullness at either or both apices, with râles and with positive sputum—provided the sputum was examined with sufficient care. It is fair to say, therefore, that if looked for in the diabetic, tuberculosis can be easily recognized in most instances. No doubt it is useful and important to have Roentgen ray films of a diabetic's chest, but because of the Roentgen ray, careful physical examination is by no means an obsolete diagnostic method.

The Prognosis of Tuberculosis and Diabetes. The ultimate prognosis of diabetes and tuberculosis, as judged by our experience, as well as by that of others, is not good. Of our 35 cases recognized from October, 1922, to January, 1929, 30 (86 per cent) are now dead. This figure in itself demonstrates how ominous is this particular combination of diseases, for nowadays patients with uncomplicated diabetes are expected to live as long as anyone else. When the tuberculosis is discovered, its subsequent course is often rapid and progressive in spite of all effort. According to our experience,

the usual duration of a diabetic patient's life after an active pulmonary tuberculosis is once discovered is illustrated in the following table:

TABLE I.—THE DURATION OF LIFE IN DIABETES AFTER TUBERCULOSIS IS RECOGNIZED.

(30 FATAL CASES.)

One year or less	19 cases (63 per cent)
More than one year and less than three years	7 cases (23 per cent)
More than three years	4 cases (13 per cent)

Certain cases get well but they must be rare. We have seen but one with this good fortune. A man, aged fifty-two years, came to the Outdoor Department in October, 1927, weighing 160 pounds and with diabetic symptoms of about a year's duration. A Roentgen ray of the chest revealed no abnormality.

He was advised to eat a diet which did not keep him sugar free but which resulted in making him lose 20 pounds in weight during the following three months. During this interval he developed cough, chest signs, positive sputum and a lesion at the right apex. As measured by Roentgen ray the process extended as low as the level of the fourth rib.

When the tuberculosis was recognized the man was treated in a less haphazard fashion. He was put in bed at absolute rest for a period of six weeks, and was then advised to resume his activities very conservatively. He was given a liberal diet and enough insulin to prevent glycosuria. Now, more than two years later, he has no signs of tuberculosis. Physical and radiologic examinations are negative and the diabetes is controlled.

Our cases bring up another practical point in prognosis. Of the four patients which have lived the longest after active tuberculosis was discovered, three gave evidence, by their histories or radiologic examinations, of having an obsolete pulmonary lesion which had become reactivated. Sosman and Steidl have commented on the dangers of the acute type of tuberculosis which they observed so frequently. This appears to have the worst prognosis. Perhaps an old focus of tuberculosis in a diabetic may protect that patient later from so virulent an infection as may develop in those diabetics unfortunate enough to acquire tuberculosis. The finding of old lesions by Roentgen ray in a diabetic's chest, therefore, is a good sign rather than a bad one, and even though the lesion becomes active, the prognosis is not as bad as in those cases with an entirely fresh process.

The Treatment of Diabetes and Pulmonary Tuberculosis. There is little to be said about the treatment of diabetes and tuberculosis. The patients certainly require the best of diabetic care, an adequate diet, and sufficient insulin to keep the urine sugar-free. They also require the best of care for tuberculosis with rest and fresh air for a

long period of time. Pneumothorax in one of our cases was not helpful.

Most of our patients were sent to one of the sanatoria after a period of observation in the Peter Bent Brigham Hospital. Follow-up notes by the various doctors who cared for them in various ways later, are all of much the same tenor. In spite of any therapy the tuberculosis advanced and the patients died. I can discover no reason for thinking that insulin was in any way harmful as a therapeutic agent to any case, nor that the tolerance of any increased during the course of the tuberculosis in such a remarkable fashion as to suggest the formation of parainsulin according to the idea of Lundberg.¹³

Summary and Conclusion. On the whole, the complication of pulmonary tuberculosis is indeed a serious one for the patient with diabetes. At the present time there are probably in the neighborhood of sixteen thousand diabetics in this country afflicted with active pulmonary tuberculosis and of these more than half are likely to die within the first twelve months after the correct diagnosis is established.

Pulmonary tuberculosis is particularly prone to develop in the elderly diabetic, of poor circumstances, leading a sedentary life, who has been at one time obese and through inadequate treatment for diabetes has lost weight rapidly. The tuberculosis may begin deep in the hilum region of the lung and at first may cause no signs or symptoms. Before long, however, the tuberculous diabetic will develop the usual signs of pulmonary tuberculosis with positive sputum. The pulmonary lesion in its beginning may be unrecognizable except by the Roentgen ray, but later can be detected easily by ordinary physical diagnosis.

Tuberculosis may develop in a diabetic patient while the patient is under treatment. It is very important for any doctor or clinic treating diabetic patients to remember this and to be on the lookout for a developing pulmonary tuberculosis. A patient under treatment for diabetes who does not hold his weight or who does not appear to be getting along satisfactorily should be suspected of having tuberculosis. All diabetic patients should be watched carefully and should have repeated physical examinations from time to time in order to forestall future complications.

The treatment of pulmonary tuberculosis according to the experience of the Peter Bent Brigham Hospital cases is unsatisfactory. At best, it is time consuming and expensive, for it requires unlimited rest, fresh air, and, in addition, adequate diabetic treatment for a long period of time. There may be apparent temporary improvement under any appropriate therapy but the final prognosis is poor. Our cases which lived the longest were those which had a quiescent pulmonary process antedating the diabetes. Later this became active, but was more amenable to treatment than the fresh type of

tuberculosis developing as a late complication of diabetes in an unresistant individual.

In future it may be possible to establish preventive measures against the occurrence of tuberculosis in diabetic patients. The first step in such a campaign, however, is to admit that at the present time tuberculosis is not infrequently encountered in diabetic patients, that it is often overlooked and treated improperly, and that it is an extremely grave complication. Cases must be recognized earlier than they are recognized at present, they must receive more serious consideration than they receive at present by doctors in the country at large, and once recognized, they must be given immediately all the benefits of the constantly improving methods of treatment which are being developed in the independent fields of the two diseases.

REFERENCES.

1. Morton, R.: *Phthisiologia*, London, Smith and Walford, 1694, p. 360
2. Nicolas and Gueudeville, V.: *Recherches et expériences médicales et chimiques sur le diabète sucré ou la phthisie sucrée*, Paris, Mequignon l'aîné, 1803, p. 99.
3. Copland and Bardsley: Quoted from Péronne.
4. Bertail: *Étude sur la phthisie diabétique*, Thèse de Paris, 1873. Quoted from Sauvage.
5. Bagou, A.: *La tuberculose pulmonaire dans le diabète sucré*, Thèse de Paris, 1888, p. 70.
6. Sauvage, R.: *Du diabète sucré dans ses rapports avec la tuberculose pulmonaire*, Thèse de Paris, 1895, p. 101
7. Péronne, V. M. E.: *La tuberculose pulmonaire du diabétique*, Thèse de Paris, 1924, p. 141.
8. LeNoir and Seherrer: *Un cas de diabète juvénile compliqué de tuberculose pulmonaire traité par l'insuline et le pneumothorax artificiel*, Bull. et mém. Soc. méd. d. hôp. de Par., 1927, 51, 1020.
9. Wilder, R. M., and Adams, S. F.: Personal Communication. See Mayo Clinic Bull., 1929, 4, 192.
10. Joslin, E. P.: *The Treatment of Diabetes Mellitus*, 4th ed., Phila., Lea & Febiger, 1928, p. 998.
11. Adams, S. F.: *The Seasonal Variation in the Onset of Acute Diabetes*, Arch. Int. Med., 1926, 37, 861.
12. Sosman, M. C., and Steidl, J. H.: *Diabetic Tuberculosis*, Am. J. Roentgenol. and Radium Therap., 1927, 17, 625.
13. Lundberg, E.: *Études sur le diabète accompagné de tuberculose*, Acta med. Scandinav., 1925, 62, 1.

SOME OBSERVATIONS ON MITRAL STENOSIS AND MEASUREMENTS OF NORMALS AMONG CHINESE.

BY OTTO WILLNER, M.D.,

YALE UNIVERSITY DEPARTMENT OF HEALTH, NEW HAVEN, CONN.

(From the Department of Medicine and the College Health Service of the Peking Union Medical College.)

DURING the last few years several Chinese patients with questionable signs of mitral stenosis were seen in this hospital. Neither roentgenogram nor electrocardiogram permitted any more definite

interpretations than the other physical findings,²³ nor did the subsequent course of the cases which could be followed add any information. But it became obvious that any attempt to draw a line between normal and pathologic findings should be preceded by a survey of the available material on both sides of the border. This survey comprised:

1. Study of the records of hospital patients with mitral stenosis, especially with regard to possible etiologic factors and prominent clinical features.

2. Mensuration and the taking of roentgenograms and electrocardiograms of normal young Chinese adults.

Mitral stenosis is often overlooked, especially in the early stage. The well-known diagnostic difficulties are best illustrated by Cabot's² statement, which is in keeping with observations of other authors; namely, that less than half of the autopsied mitral stenosis cases obtained from all services of the Massachusetts General Hospital were properly diagnosed during life.

Enlargement of the heart in a young adult implies, even in the absence of auscultatory findings, the possibility of mitral disease. To be of greatest benefit the diagnosis should be established before cardiac enlargement indicates serious, and usually, irreparable damage.

Besides the early mitral lesion of rheumatic origin there are two rarer conditions recorded in literature in which the heart, as a rule, is found to be normal or small in size, at least before complications arise, namely, Durozier's disease and spasmodic mitral stenosis. Durozier's disease, also called pure or congenital mitral stenosis,^{1, 31} gives the anatomic picture of a sclerosis of the mitral valve, often involving the pulmonary artery as well. The patients, mostly women, usually show signs of general underdevelopment. Pulmonary manifestations, especially hemorrhages, are very prominent in the clinical picture. In some of the patients tuberculosis or congenital syphilis have been encountered, but the etiologic importance of these chronic infections has not been proved.

Under the name functional or spasmodic mitral stenosis, Bard and others^{1, 21, 27, 31} have described cases in which palpatory and auscultatory signs of mitral stenosis are present only in a slight degree and not permanent. The patients often show signs of endocrine disturbances. The interpretation of the physical findings naturally remains somewhat hypothetical.

Differential diagnosis is of importance because the rheumatic lesion with its tendency to recrudescence will require a management different from that of Durozier's disease, which usually represents a stationary valvular defect; and the—hypothetical—functional mitral stenosis will require only such advice as may influence any underlying general condition.

Survey of Hospital Records. Among 24,000 patients admitted to this hospital during seven and one-half years, 95 men and 62 women were found to have mitral stenosis, as a single or combined valvular lesion. Meleney and Kellers¹⁸ call it the most common heart lesion in North China, and Dicuaide⁸ comments upon its surprising frequency. Meleney and Kellers in 1924 have reviewed the histories of 35 Chinese patients with mitral stenosis and have commented on the low incidence of typical rheumatic fever, and from subsequent observations on a larger scale in this hospital the impression is gained that severe involvement of the joints so familiar to American and British writers is very rarely seen among Chinese afflicted with rheumatic fever.

In the present survey, which includes Meleney and Keller's cases, no attempt was made to discriminate between a history of swollen joints and pains in the extremities marked enough to implant itself in the patient's memory. So-called growing pains and fleeting transient joint affections are even more characteristic of rheumatic fever than marked arthritic manifestations.

Duckworth's¹⁸ rheumatic antecedents, namely, rheumatic fever, arthritis and chorea, were recorded in the past history of this series in about the same percentage (46 per cent) as stated by Meleney and Kellers. This conforms with the figures reported from Romberg's²⁴ and Plesch's²² 1500 cardiac cases in Munich and Berlin respectively, but contrasts with Cabot's observation of 78 per cent rheumatic arthritis and 6 per cent chorea, that is, 84 per cent, or with Duckworth's 70 per cent rheumatic antecedents.

Naturally anamnestic data are an even more precarious basis for differentiation between the various forms of acute joint affections than actual clinical observation would be ——— a source of error common to all statistics mentioned above.

A frequent manifestation of mitral stenosis found in this series was hemoptysis. About 40 per cent of the patients stated that they had either frank spitting of blood or only blood-streaked sputum. Chien³ commented upon similar observations among Chinese from Changsha. Cabot found in almost half of his autopsies evidence of pulmonary infarction, although his clinical material showed a much lower incidence of hemoptysis.

In our series of cases careful and usually long observation ruled out any important pulmonary tuberculous lesion. Only 17 out of 162 cases showed shadows in the roentgenogram suggestive of hilum or minimal tuberculosis. Only 9 of these 17 had had hemoptysis. If we further compare this incidence of a little over 10 per cent with the incidence of 17 per cent as found in routine roentgenograms of 350 doctors, students and nurses examined in this hospital during the last eight years, it does not seem probable that the hemoptysis in our cases was, as a rule, due to pulmonary tuberculosis.

The incidence of syphilis among these patients—the diagnosis

based on a positive Wassermann reaction—of 14.2 per cent was not higher than found in previous surveys among medical patients and healthy employees.

As Meleney and Kellers have stated in their survey the cases of the present series are as a whole to be classified as rheumatic heart disease.

In three instances history and physical findings resembled those described by Durozier, but verification by autopsy was not available. In the 16 autopsies of this series obtained so far in this hospital, distribution and gross appearance of the valvular lesion did not differ essentially from the picture of rheumatic heart disease. Aschoff bodies were recorded in 4 of the 16 cases of long-standing.*

TABLE I.—HOSPITAL RECORDS.

	Males.	Females.
Rheumatic fever or joint pains or chorea	28	15
Hemoptysis	21	14
Positive Wassermann reaction	6	2
Rheumatic antecedents and hemoptysis	13	7
Rheumatic antecedents and positive Wassermann	1	2
Hemoptysis and positive Wassermann	4	1
Rheumatic antecedents, hemoptysis and positive Wasser- mann	4	2
Negative history	18	19
Wassermann not done	4	7
Total	95	62

<i>Males.</i>	Per cent.
Rheumatic antecedents in 46 cases	48.6
Hemoptysis in 42 cases	44.2
Positive Wassermann reaction in 15 out of 91 cases	16.5
<i>Females.</i>	Per cent.
Rheumatic antecedents in 26 cases	42.0
Hemoptysis in 24 cases	38.7
Positive Wassermann reaction in 7 out of 55 cases	12.7

Mensuration of Normal Chinese. During the last twenty-five years an increasing number of observers has emphasized the coincidence of certain types of cardiac measurements and electrocardiograms with certain constitutional features. From the various methods of mensuration Martinet's¹⁶ morphologic index (M.I.) was chosen as a simple and sufficiently accurate expression of the individual habitus or build.

Martinet calls M.I. $\frac{\text{height}}{\text{biaxillary diameter}}$.

The biaxillary diameter is measured by a ruler to which branches are attached at right angles. These are held by the subject in both axillæ with the arms hanging down while in expiration. The ratio given by Martinet is:

- (a) Below 5.5 for the brevilinear (stocky) type.
- (b) 5.5 to 6 for the mediolinear (average) type.
- (c) Above 6 for the longilinear (slim) type.

* An object of further study.

In the present series the biaxillary diameter was determined in a way somewhat different from that introduced by Martinet. Calipers were used and the transverse diameter determined in the intermediate respiratory phase. It was taken at the level of the fourth sternocostal junction in accordance with the agreement for international measurements (Duckworth)⁹. Our index figures would therefore be expected to be at a slightly lower level than if measured by Martinet's original method. In our use the term morphologic index should therefore be understood with this modification in mind.

One hundred and fifty apparently healthy young Chinese adults, 105 men and 45 women, were selected for these examinations from our students, nurses and doctors. Their birthplaces comprised nearly all of the provinces of China, a few were born on the Pacific islands or on the American continent. Their ages varied between nineteen and thirty-four. None of them had been under observation for less than one year, the majority for several, up to eight years. Among them only one brevilinear and 12 medioliner subjects were found. The rest of the 137 longilinear indices were evenly distributed between the sexes in the proportion of their numbers at the various levels. (See Charts II and III.)

Roentgenograms of Normal Chinese. Roentgenologic examination consisted of the three usual methods: (1) fluoroscopic examination; (2) stereoscopic chest films at 5 feet distance and (3) a teleoroentgenogram of the heart at 2 meter distance, exposure one-tenth second with the subject facing the film and breathing quietly. Orthodiagrams were not available.

The composite heart size was found to be slightly smaller—less than 3 sq.cm. per person—than the average size computed for Americans from height, weight and age.^{11, 12} In these statistics it was found that the subjects were divided with respect to the foreign standard of heart size as shown below.

No.	Sex.	Relation to American standard.		
		Above.	Normal.	Below.
105	Males	28	12	65
45	Females	13	4	28

Fourteen men and twelve women showed a marked dextroposition of the heart with 40 per cent or more of the horizontal diameter being found to the right of the midline.

Vertical position or cor pendulum, of varying degrees, was pronounced in about one-third of the cases. It was attempted to express the degree of "verticality" by the size of an angle V between the midline and a line drawn from the cardiac apex to the point at which the midline crosses the aortic arch (Fig. 1).

The longer the ascending aorta the smaller this angle V will be. In normal hearts, Chinese or foreign, the angle V was usually found

to be between 24 and 28 degrees. Hearts with an angle of 20 degrees or less give the impression of being unusually erect. In this study 32 men and 15 women were found to have angles between 6 and $19\frac{1}{2}$ degrees.

The angle h between the longitudinal axis of the heart and the long axis of the body was in close agreement with Kreuzfuchs' ¹ average of 48 degrees in women and 52 degrees in men.

Van Zwaluwenberg and Warren's ²⁹ auriculoventricular ratio expressed as $A-V$ index = $\frac{D O}{O G^1}$ measured in terms of their longi-

tudinal diameters in the roentgenogram was often found to be high in our series.

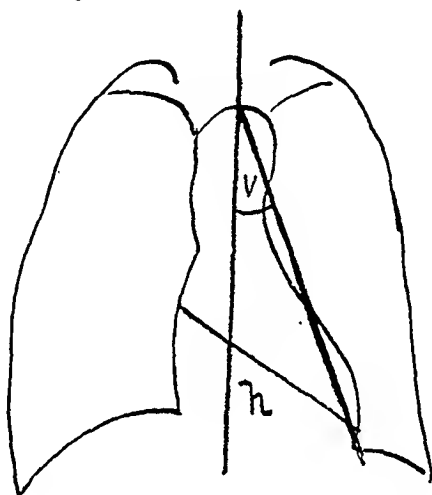


FIG. 1.—Angle expressing "verticality" of heart.

A high index is found in hearts with large auricular areas, for example, in mitral stenosis, and in individuals of asthenic build whose hearts often show the so-called mitral configuration in the roentgenogram.

About half of the subjects, males and females, examined, showed a high $A-V$ index, as seen in Chart I and Table II.

Chart II illustrates the frequent coincidence of a high morphologic index with a mitral configuration of the heart. The possible error in measuring the distances $D O$ and $O G^1$ in Fig. 2 is slight as the line $G D^1$ approximately corresponding to the auriculoventricular groove was drawn after examination by all three methods in common use. But since these measurements are derived from a photograph taken in frontal plane only it is realized that the position of the longitudinal cardiac axis should be taken into consideration. Rotation of this axis toward the sagittal plane, as it may occur for instance in a deep but narrow thorax, would produce a smaller and narrower cardiac shadow and may alter the auriculoventricular ratio.

A number of authors, among them Vaquez and Bordet, have considered this point and have advocated roentgenologic examination in both oblique diameters. Danzer,⁵ Martinet¹⁶ Moritz¹⁹ and others have demonstrated the relationship of heart measurements to the dimensions of the thorax. Morphologic characteristics of the Chinese will have to be taken into account before a standard for them can be established. For the time however, a comparison of our measurements with those obtained on Europeans and Americans by the same standard laboratory methods³² was the chief object.

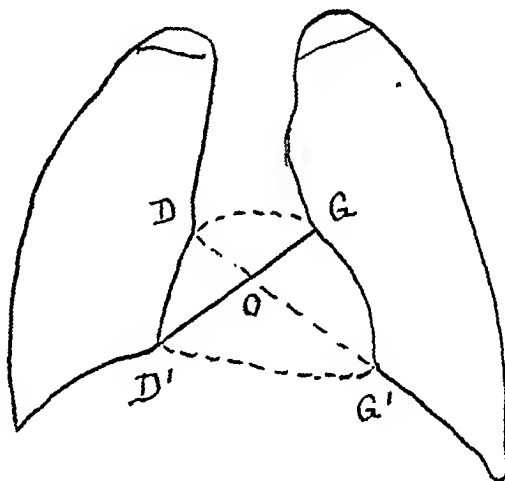


FIG. 2.—Auriculoventricular ratio.

Taken from Vaquez and Bordet:³⁰ The Heart and the Aorta

$\frac{DO}{OG'}$ normally 0.53 to 0.70.

Below there is a summary of Charts I and II, showing the prevalence of longilinear build and the high incidence of mitral configuration. Both qualities are slightly more pronounced in women than in men.

TABLE II.—CORRELATION OF HABITUS WITH AURICULOVENTRICULAR RATIO.

No.	Habitus.	Ratio D O : O G ₁ .		
		Low.	Normal.	High.
<i>Males.</i>				
1	Brevilinear	1		
10	Mediolinear	1	6	3
94	Longilinear	4	45	45
<hr/>		<hr/>	<hr/>	<hr/>
105	<i>Total males</i>	6	51	48
<i>Females.</i>				
0	Brevilinear.			
2	Mediolinear	2
43	Longilinear	2	19	22
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45	<i>Total females</i>	2	19	24
150	<i>Both sexes</i>	8	70	72

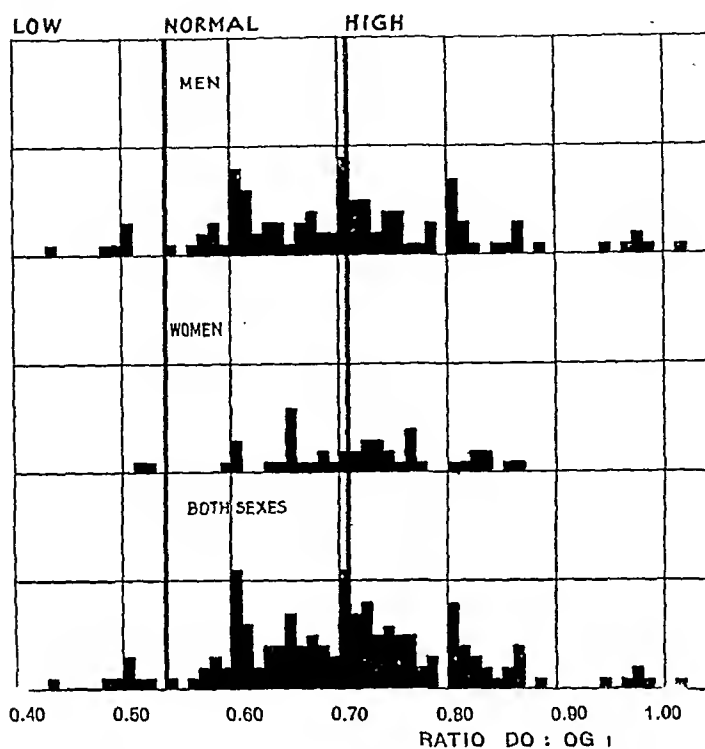


CHART I.—Auriculoventricular ratios in Chinese. The auriculoventricular ratios (D O : O G) are indicated by the black squares. The heavy lines enclose the normal range (0.53 to 0.70). Note the prevalence of high ratios.

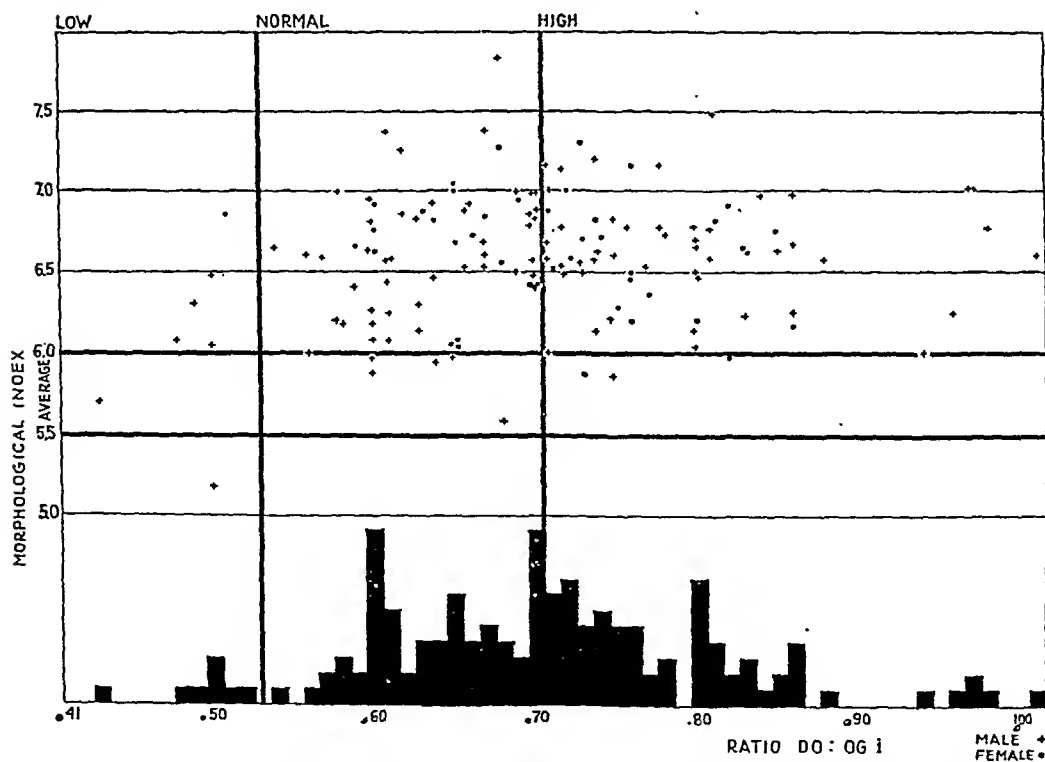


CHART II.—Correlation of morphologic index with auriculoventricular ratio. The auriculoventricular ratios are indicated by the black squares at the bottom of the chart. The morphologic indices by crosses and points. The heavy lines enclose the normal ranges. A-V = ratio : 0.53 to 0.70 • M.I. : 5.5 to 6.

Electrocardiograms. The hypertrophy of the left auricle and of the right ventricle characteristic of mitral stenosis often finds an expression in the electrocardiogram. Notching or enlargement of the *P* wave in both directions and right ventricular preponderance are frequently recorded. Right ventricular preponderance can, however, be produced by a number of other factors and is therefore not pathognomonic of mitral stenosis.

Kraus and Nicolai¹³ have for example commented upon the occurrence of S_1 in the electrocardiograms of children and of persons of asthenic build. The two authors demonstrated experimentally, in collaboration with E. Meyer,¹⁴ the appearance of S_1 as the result of measures which produced a lowering of the blood pressure.

Meek and Wilson,¹⁷ experimenting on dogs, have demonstrated that rotation of the heart around its longitudinal axis is more apt to produce deviation of the electrical axis than cardiac displacement to the right or left.

Stoss²⁶ has recently reported the correlation of different types of the initial ventricular complex with certain anthropologic characteristics. As this, the *Q-R-S* complex, usually contains the highest peaks in the electrocardiographic curve, it also is used for determination of the electrical axis, and Stoss' types represent merely a scale of electrocardiograms with various angles of the electrical axis, which may be useful for quick orientation.

None of the electrocardiograms of the 150 health subjects of this series showed any important departure from the normal curve. Two of them showed a slight widening of the *Q-R-S* complex to 0.08 seconds. The determination of the angle of the electrical axis; that is to say the direction of potential at the time of the height of the *R* wave, was done by Dieuaide's method.⁷ This angle is included between the line which represents the direction of the potential and the horizon.

The findings which were entered on Chart III showing the angle on the abscissa and the morphologic index on the ordinate conform, as a whole, with Stoss' observation which, expressed in other words, tells that the normal electrocardiogram of the asthenic individual shows generally a tendency to right, that of the stenic individual a tendency to left ventricular preponderance.

The occurrence of right ventricular preponderance in 4 per cent of apparently healthy persons is noteworthy. Another 4 per cent showed angles between 0 and 30 degrees, which may be considered as a slight tendency to left ventricular preponderance.

While accepting angles between 0 and 90 degrees in accordance with Greene and Carter's statement⁷ as the normal range, the prevalence of large angles is striking; 97 out 150 persons had angles above 60 degrees. Only 6 of these 97 persons were of medioliner build. Each of the 6 persons with angles above 90 degrees showed

the so-called mitral configuration of the heart with high auriculo-ventricular index (between, 0.74 and 0.94) by teleoroentgenogram.

Comment. The etiologic history of Chinese patients with mitral stenosis of the rheumatic type conforms mostly to that of cases observed in central Europe, but the comparatively slight involvement of the joints in contrast to the severe cardiac damage resembles the course of the disease in young children. Meleney and Kellers discuss among other points the possible influence of the vegetarian diet of the Chinese upon their susceptibility for arthritis.

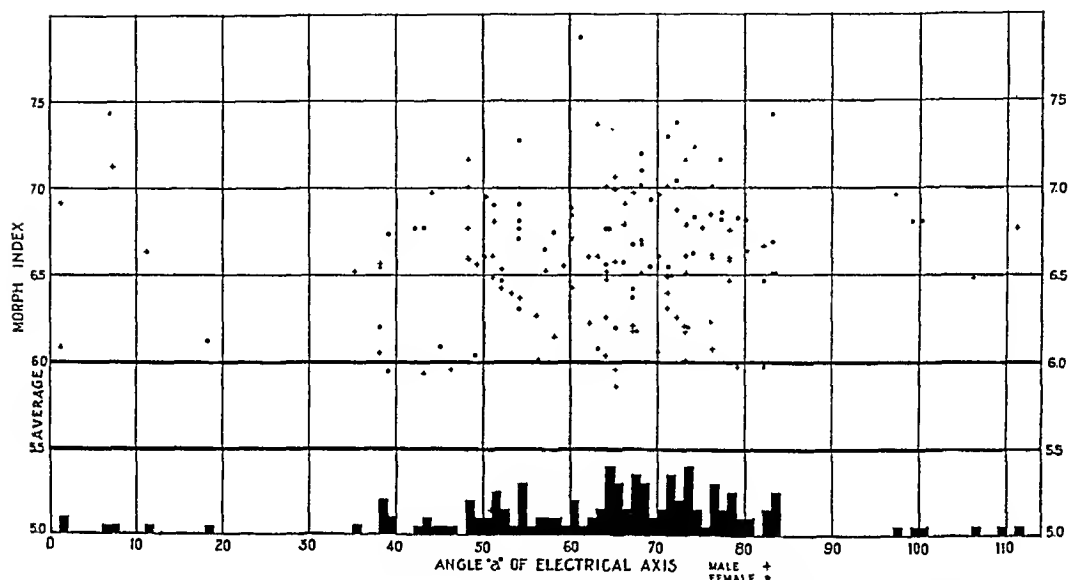


CHART III.—Correlation of morphologic index with angle of the electrical axis. The angles of the electrical axis are indicated by the black squares at the bottom of the chart, the morphologic indices by crosses and points. The heavy lines enclose the normal range of the M.I. : 5.5 to 6.

Hammond and Hsia Sheng¹⁰ and Holt and Hammond* found the incidence of dental cavities among Chinese orphans to be about 10 times lower than among a similar group of American school children in Peking. This observation fully conforms with the findings on routine health examinations of the students and nurses of this college.† The lower incidence of foci of infection at an age which usually coincides with the most active period of rheumatic fever may have some bearing upon its manifestations. The high incidence of hemoptysis, similar to that observed in Durozier's disease, points to the presence of other peculiar factors, for instance, in the pulmonary circulation, as a counterpart to the relative hypotension observed among Chinese.²⁸

The various measurements on normal persons made in these studies serve merely as mathematical expressions of different types

* Personal communication by J. W. Hammond.

† Personal communication by B. G. Anderson, D.D.S.

of build, cardiac outline, and electrocardiogram. These types are easily recognizable by inspection which in this way acts as a control against gross errors.

The features characteristic of Kraus' heart of the narrow chested, namely, a long, narrow heart, in median, vertical position with a long aorta, mitral configuration, and a large angle of the electrical axis, viz., tendency to right ventricular preponderance, were rarely encountered in their totality in any single subject. The majority of the hearts examined presented, however, one or several of these characteristics. Study of measurements of the various thoracic diameters and the position of the heart would be helpful in establishing standards for comparison. Mensuration of Chinese brought up in foreign countries could decide the question whether the prevalent characteristics found in this series should be considered as racial traits or be ascribed to environmental factors.

In several respects the observations recorded resemble Martinet's hyposphyxia, a circulatory symptom complex closely connected with longilinear build and circulatory dystrophy. Mitral stenosis is one of the diseases in which Martinet finds the hyposphyxic syndrome consisting of low arterial systolic and low pulse pressure together with increased venous pressure and increased blood viscosity. The latter two factors, for which Martinet recommends specific methods of examinations, could not be determined in this investigation.

Attempts to distinguish between mere mitral configuration of the heart shadow and true mitral stenosis have been based chiefly upon visualization of the enlarged left auricle in profile^{60,25,31} with or without contrast filling of the esophagus. The number of complete observations including autopsy is as yet too small to permit a definite evaluation of these methods in differential diagnosis.

Extensive studies of the anatomy and physiology of the Chinese have begun to prepare the ground for a conception of endogenous factors in the causation of their diseases. The present investigations have attempted to present some problems of cardiac diagnosis from this viewpoint.

Conclusion. 1. The clinical picture of mitral stenosis among Chinese as obtained from a survey of 157 hospital records presents several prominent features commonly found in groups of patients, among which asthenic habitus is prevalent.

2. On examination of 150 healthy young Chinese adults a correlation could be demonstrated between three predominating characteristics, namely, asthenic build, mitral configuration of the heart, and a large angle of the electrical axis. A description of the patient's habitus, more exact and uniform than commonly used, might therefore help to evaluate the other findings in the individual case. Among the various anthropometric methods the determination of the morphologic index recommends itself by its simplicity.

3. In view of the fact that healthy persons of asthenic build often present the same type of cardiac outline and electrocardiogram as patients with mitral stenosis; and further as mitral stenosis seems to occur more frequently in persons of asthenic build, the diagnosis of doubtful cases should depend almost entirely on clinical evidence.

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LITERATURE.

1. Bauer, J.: *Konstitutionelle Disposition zu inneren Krankheiten*, 3d ed., Berlin, Springer, 1924 (Lit.).
2. Cabot, R. C.: *Facts on the Heart*, Philadelphia, Saunders, 1926.
3. Chien, M. H.: *Differential Diagnosis of Early Pulmonary Tuberculosis and Mitral Disease*, *China Med. J.*, 1928, 42, 26.
4. Cohn, A. E.: *An Investigation of the Size of the Heart in Soldiers by the Teleoroentgenogram Method*, *Arch. Int. Med.*, 1920, 25, 499.
5. Danzer, C. S.: *The Cardiac-thoracic Ratio: An Index of Cardiac Enlargement*, *Am. J. Med. Sci.*, 1919, 157, 513.
6. Dedie, St.: *Das mitral stenotische und das mitral configurierte Herz im Profil*, *Fortschr. a. d. Geb. d. Roentgenstr.*, 1928, 37, 68.
7. Dieuaide, F. R.: *The Determination and Significance of the Electrical Axis of the Human Heart*, *Arch. Int. Med.*, 1921, 27, 558.
8. Dieuaide, F. R.: *Present-day Views in Regard to Heart Disease*, *China Med. J.*, 1926, 40, 344.
9. Duckworth, W. L. H.: *International Agreements for the Unification of Anthropometric Measurements*, Cambridge University Press, 1913.
10. Hammond, I. W., and Hsia Sheng: *The Development and Diet of Chinese Children*, *Am. J. Dis. Child.*, 1925, 29, 729.
11. Hodges, P. C.: *A Comparison of the Teleoroentgenogram with the Orthodiagram*, *Am. Jour. Roentgenol. and Rad. Therap.*, 1924, 11, 466.
12. Hodges, P. C., and Eyster, I. A. E.: *Estimation of Cardiac Area in Man*, *Ibid.*, 1924, 12, 252.
13. Kraus, F., and Nicolai, G. F.: *Das Elektrokardiogramm des gesunden und kranken Menschen*, Leipzig, Veit, 1910.
14. Kraus, F., Nicolai, G. F., and Meyer, E.: *Prinzipielles und Experimentelles über das Elektrokardiogramm*, *Arch. f. d. ges. Physiol.*, 1913, 155, 97.
15. Lai, D. G.: *Incidence of Syphilis Among the Chinese Soldiers at Swatow*, *China Med. J.*, 1928, 42, 557.
16. Martinet, A.: *Morphologie corporelle et morphologie cardioaortique*, *Presse méd.*, May 15, 1920, No. 31; *Clinical Diagnosis*, English translation by de Sajous, Philadelphia, Davis, 1928.
17. Meek, W. J., and Wilson, A.: *The Effect of Changes in the Position of the Heart on the Q-R-S Complex of the Electrocardiogram*, *Arch. Int. Med.*, 1925, 36, 614.
18. Meleney, H. E., and Kellers, I.: *Mitral Stenosis Without Rheumatic Fever in North China*, *Arch. Int. Med.*, 1924, 34, 455.
19. Moritz, F.: *Zur Beurteilung der Herzgrösse*, *Fortschr. a. d. Geb. d. Roentgenstr.*, 1928, 38, 993.
20. Németh, P.: *Zur Kenntnis der Mitralform gesunder Herzen*, *Klin. Wchnschr.*, 1923, No. 8, p. 348.
21. Ortner, N.: *Spezielle Symptomatologie der Herzkrankheiten*, Krause, P., *Klinische Diagnostik*, 1913, p. 243.
22. Plesch, J.: *Die Herzklappenfehler*, Kraus und Brugsch, *Spez. pathol. Therapie*, Berlin, Urban und Schwarzenberg, 1925, 5, 2.
23. Reid, W. D.: *Comparison of the Electrical Axis Shown by the Electrocardiogram with Roentgen Mensuration of the Heart*, *Am. Heart J.*, 1928, 4, 223.
24. Romberg, E.: *Lehrbuch der Krankheiten des Herzens und der Blutgefäße*, 4th and 5th ed., Stuttgart, Enke, 1925.
25. Steel, D.: *The Roentgenological Findings in Mitral Stenosis and Insufficiency*, *Am. J. Roentgenol.*, 1929, 21, 220.

26. Stoss, M.: Ueber die klinische Bedeutung der Kammeranfangsschwankung im Electrocardiogramm und ihre Beziehungen zum Habitus, *Deutsch. Arch. f. klin. Med.*, 1927, 157, 263.

27. Strauss, H.: Ueber den Habitus asthenicus und seine klinische Bedeutung, *Berlin klin. Wehnschr.*, 1910, p. 207.

28. Tung, C. L.: Blood Pressure of Chinese in China and in the United States, *Chinese J. Physiol.*, 1928, No. 1, p. 93.

29. Van Zwaluwenberg and Warren: Diagnostic Value of the Orthodiagram in Heart Disease, *Arch. Int. Med.*, 1911, 7, 137.

30. Vaquez and Bordet: The Heart and the Aorta, English translation by Honeij and Macy, Yale University Press, 1920.

31. Vaquez, H.: Diseases of the Heart, translation by Laidlaw, Philadelphia, Saunders, 1924.

32. Wilson, F. W., and Merrill, E. F.: The Value of the Roentgen Ray in Cardiac Diagnosis, *Am. J. Med. Sci.*, 1923, 165, 340.

ALLERGIC MIGRAINE.

BASED ON THE STUDY OF FIFTY-FIVE CASES.

BY RAY M. BALYEAT, M.A., M.D., F.A.C.P.,

LECTURER ON DISEASES DUE TO ALLERGY, UNIVERSITY OF OKLAHOMA MEDICAL SCHOOL,

AND

FANNIE LOU BRITTAIN, B.S., M.D.,

OKLAHOMA CITY, OKLA.

THE migraine syndrome is a snag over which medical investigators have stumbled during the centuries past. Some of the early writers of the nineteenth century noticed a similarity between asthma, hay fever, and migraine. Vaughan¹ reported a series of cases from which it appears that migraine of all ages is often associated with a specific sensitization to one or more food proteins. His patients obtained entire or partial relief by eliminating from their diets the foods to which they were specifically sensitive. It is now generally accepted that the exciting factor in all seasonal hay fever, and practically all cases of asthma, is a sensitization to foreign proteins. One of us² in a recent work on the hereditary factor in allergic diseases, showed that migraine is interchangeable in the linkage with hay fever and asthma, which is good evidence that asthma, hay fever, and migraine, have a common etiologic factor. A study of the migraine problem from the standpoint of allergy during the past few years has certainly thrown new light on the subject. From a review of a series of cases studied by us during the last two years it appears that practically all cases of true migraine have as an exciting factor a sensitization to foreign protein, and that our treatment based on the allergic findings has given results equal to those in practically any other chronic disease. Henceforth

we believe the migraine symptom complex must be considered either curable or at least controllable in the majority of cases.

The material for this study is based on 55 cases of migraine whose ages range from six to sixty-eight years. All were private cases, American born, and about 75 per cent have been under observation from six months to two years. There were 23 males (41.8 per cent) and 32 females (58.2 per cent). The onset of symptoms occurred in 16, or 29.1 per cent, during the first decade; in 15, or 27.3 per

TABLE I.—DISTRIBUTION OF AGE OF ONSET OF CLINICAL MANIFESTATION OF MIGRAINE IN PATIENTS OF ALL AGES, BASED ON 55 CASES.

Age of onset.	No. of cases.	Percentage.
First decade	16	29.1
Second decade	15	27.3
Third decade	14	25.4
Fourth decade	10	18.2

cent, during the second; in 14, or 25.4 per cent, during the third decade, and in 10, or 18.2 per cent, between the ages of thirty and forty-six years. A large per cent of the patients were made up of housewives, stenographers and professional men. Seven of the 55 cases were physicians.

The Hereditary Factor in Migraine. Practically all investigators give heredity as the most potent factor in the production of migraine. It need not be assumed, as is frequently believed, that the hereditary factor must be migraine itself. It has been our experience that it is only one of a number of symptom complexes which are metamorphosed in passing from parent to offspring and arise in different forms in different members of a family. For example, five children in one family might be specifically sensitive to wheat. From such a sensitivity asthmatic symptoms might appear in the first child, eczema in the second, hay fever in the third, urticaria in the fourth, and migraine in the fifth. The mother of the children might have been a hay fever sufferer whose symptoms were due entirely to a sensitivity to Bermuda grass pollen, and her mother might have had asthma due to a sensitivity to cat hair. The type of sensitivity from which the antecedent suffers has no relation to the type the descendent may have. It must be remembered that we do not inherit from our parents or grandparents or anyone, so far as that is concerned. Our parents and we inherit from the same germ plasm and therefore the same plans and specifications are used in our makeup, which accounts for our having traits in common. We inherit germ cells whose chemical combination is similar. In the germ cells are determinors which decide whether or not we will have the ability to become specifically sensitive, but we do not inherit the specific allergic disease. With this ability we may become specifically sensitive to one or more food proteins and from that sensitivity develop migraine, but we do not inherit migraine itself.

In the series studied, a positive family history of allergy was elicited in 47, or 85.4 per cent. There was a family history of migraine in 25, or 45.4 per cent. In 37, or 67.3 per cent, of the cases, there were other manifestations of allergy. In other words, individuals born with the ability to become specifically sensitive to food protein and have migraine, should also under adequate contact become sensitive to inhalants and have asthma or hay fever, and from the above figures apparently they do.

Exciting Factors. From a study of the hereditary factor in migraine it seems logical to believe that the exciting factor is always a specific sensitivity to one or more foreign proteins. In every case studied a positive reaction to one or more foreign proteins, either food or inhalants, was found. By no means, however, did we feel that we found the chief offending protein in every case. The following table will show the positive food findings:

TABLE II.—OCCURRENCE OF SCRATCH AND INTRADERMAL REACTIONS TO THE MOST COMMON PROTEINS USED IN TESTING 55 CASES OF MIGRAINE.

Food reactions.	No. of cases.	Percentage of positive reactions.	Food reactions	No. of cases.	Percentage of positive reactions.
Wheat . . .	38	69.0	Tea . . .	10	18.1
Milk . . .	25	45.4	Mushroom . . .	9	16.3
Egg . . .	20	36.3	Peach . . .	9	16.3
Fish . . .	36	65.4	Lemon . . .	9	16.3
Bean . . .	33	60.0	Sweet potato . . .	8	14.5
Nuts . . .	23	41.8	Artichoke . . .	8	14.5
Turnip . . .	21	38.1	Beet . . .	8	14.5
Cheese . . .	19	34.5	Apricot . . .	8	14.5
Radish . . .	17	30.9	Grapefruit . . .	8	14.5
Parsnip . . .	17	30.9	Irish potato . . .	7	12.7
Eggplant . . .	17	30.9	Fig . . .	7	12.7
Barley . . .	15	27.2	Orange . . .	7	12.7
Asparagus . . .	15	27.2	Garlic . . .	7	12.7
Lettuce . . .	15	27.2	Vanilla . . .	7	12.7
Cabbage . . .	13	23.6	Paprika . . .	7	12.7
Buckwheat . . .	12	21.8			
Rye . . .	12	21.8	<i>Inhalants</i>		
Pea . . .	12	21.8	Feathers . . .	34	61.8
Celery . . .	11	20.0	Dog hair . . .	20	36.3
Cottonseed . . .	11	20.0	Cat hair . . .	17	30.9
Cauliflower . . .	11	20.0	Horse hair . . .	16	29.0
Cantaloupe . . .	11	20.0	Cattle hair . . .	11	20.0
Coffee . . .	11	20.0	Rabbit hair . . .	9	16.3
Spinach . . .	10	18.1	Wool . . .	9	16.3
Onion . . .	10	18.1	Orris root . . .	14	25.4
Tomato . . .	10	18.1	Pollen . . .	31	56.3

Most patients were found sensitive to a number of foods, but dietary manipulation proved in the majority of cases that one or two of the foods would be the chief offenders. Wheat was positive in 38 cases and was considered a very important factor in 14. Milk was definitely positive in 25, and was strikingly important in 6. Eggs were positive in 20, and played a very important part in 4.

Fish was positive in 36 cases; bean in 33; nuts in 23; lettuce in 15; celery in 11, and so forth. From our study it appears that the average case of migraine is sensitive to a multiplicity of food protein, and many to inhalants. This is not unlike the adult asthmatic, who is usually sensitive to a large number of foreign proteins.

Predisposing Factors. Conditions which play a part as predisposing factors are as follows: (1) Physical fatigue; (2) mental fatigue and depressed states; (3) thyroid disfunction; (4) genito-sexual cause; (5) toxic states; (6) disturbance of the special senses.

We have observed a number of patients who developed typical attacks of migraine following exhaustive physical exercise. It is very common to have the attacks follow mental strain, prolonged worry, or extreme excitement. The headaches may come on periodically with the menses or be precipitated by psychosexual excitement. Endogenous toxins, such as from infected teeth, tonsils, or toxins from an exogenous source, such as lead poisoning, or partially burned gas fumes, may bring on the headache. Refractive errors, or a disturbance of the normal hearing, smelling, seeing, or tasting, may play a part in precipitating an attack. In the opinion of the authors the above factors mentioned must be considered as predisposing factors only, just as we would consider cold air, exertion, excitement, infection in the bronchial tubes and other parts of the body, and chemical odors, as predisposing factors and not the exciting one in true bronchial asthma.

Symptomatology. The migraine attack may follow severe physical exhaustion or prolonged mental strain or worry, or extreme excitement. Such attacks, therefore, may come anytime during the day, usually without prodromal symptoms. Frequently, without any known cause, however, severe attacks of migraine may occur following a restful, sound sleep. A patient commonly awakens with a feeling of "goneness" and feels "draggy" until the latter part of the morning, when nausea and headache appear. In about one-third of our cases a feeling of nausea or abdominal discomfort was not present. In the remaining cases, however, either nausea, mild or severe, associated with vomiting, slight or marked, at some time during the attack occurred. As a rule the headache manifested itself as a sensation of mild pressure, frequently in one or both temple regions. The pressure disturbance gradually increased in area and intensity to the extent that many patients declared that they felt that the top of their skull would come off. Most patients reported that when the severity of the pain reached its peak there was no one part of the head in which the pain seemed more severe than another. Only in 9 per cent of the cases was the symptom of zigzag lights present. The severity of attacks in one patient may vary greatly from time to time, and of course the severity in different patients, like in asthma or hay fever, varies greatly. Many suffer from pain, nervousness and exhaustion to the extent that they are

confined to their beds during a small part or most of the time the attack is on. The duration of their attacks averaged two days. Many reported light attacks of only a few hours, and other attacks lasting four to five days. The frequency of their attacks occurred from a few days to a year, the average being fifteen days. Some patients reported that they were never free from a dull headache between the paroxysms of attacks.

A brief review of the following cases seems justified, as from them will be illustrated many points previously discussed and that will be subsequently mentioned.

Case Reports. CASE I.—M. A. B., a man aged forty-five years, had suffered from very severe attacks of migraine since eleven or twelve years of age. During the past eighteen years his attacks occurred on the average of every two weeks, and lasted from two to three days. The severity of his attacks was such that at least one day during the period he was unable to work.

He had one maternal uncle with asthma; the maternal grandfather with asthma, and the mother had eczema. During his early life he had hives on a number of occasions, but except for his migraine he has never consulted a physician since a small child.

He is a stove manufacturer and lives a very busy life and one that requires a great deal of mental strain. It was interesting to have him tell how his headaches had interfered with his work. He said, for example, that he would have an appointment with a wholesale house to discuss the subject of the sale of his product, and by the time his appointment would occur he would frequently be in bed with a severe headache.

Scratch and intradermal methods of testing revealed the following: milk ++; cheese +; codfish +; crab ++; salmon +.

An outline concerning his diet was given him, in which there were excluded from the diet milk and all milk products, and all shell sea foods, but no other foods. This man was first seen two years ago, and since that time he has had but one attack except on two occasions when he was at the seashore and ate heavily of sea foods, and reported rather severe typical migraine attacks.

This case illustrates a type of migraine in a business man who has had his business very seriously interfered with by the severity of the attacks. This is not an unusual case. It also illustrates the effect of anxiety and mental strain. He is sure, as he states from trying it out, that taking the offending foods will bring on attacks and that when he leaves them out of his diet his work may be very heavy and there may be considerable mental strain, but he will remain free from migraine attacks.

CASE II.—Mrs. W. T. C., housewife, aged thirty-four years, had suffered from seasonal hay fever nine years, migraine since in the teens, and a severe colitis for fifteen years. She was a very nervous patient. She had been under the care of a number of physicians, including the neuropsychiatrist, the gastro-enterologist, and the rhinologist, but had found little relief. Her attacks of migraine were only moderately severe at times, but were quite frequent. At other times they were very severe and there were present many of the signs which occur in true migraine, namely, severe headache, nausea, vomiting, zigzag lights, marked prostration.

Scratch and intradermal testing revealed a positive reaction to a large number of foods, the chief of which were eggs, buckwheat, beans, celery and cantaloupe, and a marked reaction to ragweed and a number of the grasses.

The positive foods were eliminated from her diet with a result of practically complete freedom from the migraine and complete freedom from colitis. She is being desensitized at present against the ragweed as a means of preventing her seasonal hay fever.

This case illustrates one who has three manifestations of allergy, namely, hay fever, mucous colitis, and migraine. It is quite possible that the chief etiologic factors in her migraine and mucous colitis are the same. Her hay fever is seasonal in type and the chief factor is pollen. However, it would be folly to treat this individual for her hay fever without eliminating the foods to which she is specifically sensitive and which are causing the other allergic manifestations. She has learned that partaking of the forbidden foods will bring on attacks and leaving them off will give her freedom.

CASE III.—A. W. H., merchant, aged thirty-eight years, came to our Clinic with a history of recurrent attacks of severe headache, which started in childhood. His maternal grandfather had migraine. He was told that he could not take milk and remain free from headaches. The patient's past history was entirely negative from the standpoint of disease except for headaches. His trouble first began as a very small child, disappearing around twelve but recurring again at twenty-two. The attacks are from three to four days' duration and occur about once a month. The pain is very severe over one eye only. It is stabbing in character and apparently goes through to the other side of the head. He has learned that extra work, especially mental strain, will help to precipitate an attack.

Very careful food testing revealed a sensitivity to milk only. Milk was removed from his diet, with complete relief except for one or two times that he has taken less than a teaspoonful of milk just to try it out and has found this sufficient to bring on a headache attack.

Most patients who have migraine are sensitive to a multiplicity of proteins. This man, differing from the rule, however, was found sensitive only to milk.

CASE IV.—K. W., a physician, aged thirty-eight years, developed severe attacks of migraine at the age of thirty-six. His attacks were very severe and he had all of the symptoms which occur in migraine. He had noticed a number of foods which he was sure helped in provoking an attack. He has hay fever and some asthma. His maternal grandmother had migraine, his father had mucous colitis.

On testing him we found him extremely sensitive to a very large number of foods, including the following: Wheat and its split products +++; coffee ++; bean +++; kidney bean ++++; turnip ++++; asparagus ++; celery ++++; tomato ++; garlic ++++; peach ++++; orange ++++; grapefruit ++; pineapple ++++; lobster ++; clam ++; crab ++; almond ++; peanut ++++; hickory nut ++++; vanilla ++; parsnip ++++; ginger ++++.

A careful elimination of the foods to which he is specifically sensitive has given this physician freedom from attacks during the last eight months, except for two. One followed a lawsuit, during which there was a great deal

of excitement and mental strain, and the other following a hunting trip, during which time he was physically exhausted and had eaten some wheat bread.

This case illustrates the effect of the predisposing factor, such as mental strain and physical exhaustion, and also the effect of the exciting factor, such as the eating of the specific foods to which he is sensitive. It is interesting to note that his trouble started in the third decade. From our findings it appeared that about an equal number developed symptoms in the first, second, third and fourth decades.

CASE V.—Mrs. W. R. B., housewife, aged thirty-one years, gave a history of migraine since she was thirteen years of age and hives at intervals since a small child. She had one brother with hay fever; one sister with hay fever; her mother had migraine; her maternal grandfather had migraine, and her father had hives. She gave a history that her migraine occasionally would occur during the intramenstrual period but usually would occur just previous to the menses and would commonly be so severe, along with her menstrual period, to require her to remain in bed during a large portion of the period.

Food testing gave a reaction to the following proteins: Casein ++; coffee +; blackeyed pea ++; pork +; raspberry +++; wheat ++.

Elimination of the offending proteins has given this patient entire freedom from her trouble.

This patient illustrates the type who have their attack of migraine frequently coincident with the menstrual period or occurring just before. This is not unusual. The nervousness near the menstrual period is not the exciting factor but the predisposing cause. When the exciting factor is eliminated, as was done in her case, namely, the elimination of the foods to which she is specifically sensitive, the nervousness of the menstrual period produced no headache.

Discussion. In all the cases presented, and as has been previously mentioned, in a large per cent that we have studied, there is a definite hereditary history of migraine or other allergic manifestation, namely, asthma, hay fever, eczema, urticaria, and chronic colitis. Of the 5 cases presented, which are typical of the majority studied, the predisposing factors, such as those previously mentioned in the article, seem to play a definite part in bringing on the attacks of headaches, but these 5 patients, along with a majority of the others studied, reported that when they adhered strictly to their diet they were free from headaches in spite of physical exhaustion, mental strain, menstrual periods, and the like. In allergy this parallels Koch's postulates as applied to bacteriology and is a very necessary antecedent to the acceptance of the theory as to the exciting factor.

General Health and Mental Activity of Migraine Patients. In our study of migraine patients we have been impressed with the fact that their general health is usually above the average. The syn-

drome occurs more commonly in a class of people whose vegetative nervous system is highly developed, most of whom are very active mentally. The symptom complex is not commonly found in the negro, Indian, or among the Chinese. In these races allied allergic manifestations, namely, hay fever, asthma, urticaria, and certain forms of eczema and colitis, are comparatively infrequent.

Methods of Testing for Exciting Factors. The scratch method of testing should first be used. All questionable reactions should be checked by the intradermal method. If only the scratch method is used, many proteins to which the patient is specifically sensitive will not be found. Treatment outlined on such findings therefore would not give results. An immediate reading should always be made, but also a four and a twenty-four-hour reading should be made, since delayed reactions are common. Food reactions in migraine, like those in eczema and urticaria, are difficult to read. One must always take into consideration the variable reactivity of different skins.

Multiple sensitivity is the rule. All patients except one in our series were found sensitive to more than one protein. Such a finding is true in other allergic syndromes. Multiple sensitivity should be the rule, since an individual born with the ability to become sensitive to one food protein naturally should become sensitive to others, especially if they have partaken of them in large amounts.

Differential Diagnosis. Migraine must be differentiated from functional headaches, trifacial neuralgia, myalgia, ordinary intoxication and infections, such as those of alcohol, tobacco and uremia, and from headaches due to pituitary disfunction. A clear-cut history of periodic headaches over a long period of time, with freedom between, and especially with a history of the usual prodromal symptoms spells migraine. In those cases in which the onset has been recent of course the differential diagnosis is a little more difficult. In making a differential diagnosis a familial history of allergic diseases should be given much weight, that is, if the headache is somewhat an atypical one and the familial history is great, one should be careful in not diagnosing the headache as a migraine one, while on the other hand if the symptoms are not clear cut and the family history is negative so far as allergic diseases are concerned, one should be careful in calling the headache migraine in type.

Prognosis. It is generally taught that migraine of all types gradually disappears in the third and fourth decades and that there are only few exceptions to this rule. From our study this appears not to be true, since of the 55 cases 7, or 12.7 per cent, came seeking relief during their sixth decade. From the standpoint of life and death, and also complications, prognosis of course is good. The complications that occur in many are those of other allergic manifestations, especially eczema, asthma and hay fever.

Treatment. Until relatively recent times migraine was placed by the medical profession in the category of uncontrollable human ailments. As many remedies as there are drugs in the pharmacopeia have been suggested for it but their efficacy is in inverse proportion to their number. Until the last decade much attention was given to the predisposing factors but too little attention has been paid to the exciting causes. This was likewise true of the other allergic syndromes. However, since the recent discovery of exact means of determining the exciting factors in each case more attention to the disease is being given by the medical profession.

It is obvious, in the first place, that the predisposing factors should be eliminated. For example, plenty of rest and sleep should be taken by the sufferer. Avoidance of physical exhaustion, mental fatigue and worry is always in order. Toxic states should be sought for and eliminated if found. Correction of refractive errors and any errors of the other special senses should be done.

When all the foregoing measures have been taken many patients will be somewhat better, but the vast majority will continue to have their migraine. Not until the exciting factor, namely, the foods to which they are specifically sensitive, is removed from their diet, can one hope for good results. All of the foods to which a patient is found definitely sensitive should be removed from the diet. In some cases it is impossible to find them by testing, or at least all of them. In such patients eliminative diets, based on our knowledge of the most common food factors in other cases, are used. Other foods are added or subtracted from time to time as a means of determining the offending food.

In our series of 55 cases, 29, or 52.7 per cent, obtained from 85 to 100 per cent freedom from symptoms, which we consider excellent results. There were 10, or 18.2 per cent, who received more than 60 per cent relief, which we classify as good results. Another 11, or 20 per cent, received more than 40 per cent relief, which we considered fair results. In 5 cases we were able to give less than 40 per cent or no relief, which we considered poor results.

From our findings it appears that the results in the treatment of migraine are as good or better than those obtained in nearly any other chronic disease. The average migraine patient who receives more than 80 per cent results, practically speaking is well so far as the symptoms interfering seriously with his comfort or his carrying on a gainful occupation is concerned. Those cases who receive more than 60 per cent relief frequently are changed from very uncomfortable people, unable to carry on a gainful occupation, to comfortable, practical individuals. Even those who received 40 per cent relief were grateful patients. From our findings we are led to believe that the exciting factor in migraine is a specific sensitivity to food, which can be found in the majority of cases, and the treatment based on such findings gives results that are well worth while.

Summary. 1. A family history of allergy was elicited in 85.4 per cent of the cases.

2. From a study of the hereditary factor in migraine it appears that it is interchangeable in the linkage with asthma and hay fever, which is good evidence that these syndromes have a common etiology, namely, a specific sensitization.

3. The exciting factor in migraine is probably always a specific sensitivity to one or more foreign proteins.

4. There are many predisposing factors, such as (a) physical fatigue; (b) mental fatigue and depressed states; (c) thyroid disfunction; (d) genitosexual cause; (e) toxic states; (f) disturbance of the special senses.

5. The onset of symptoms occurred in nearly one-third of the cases during the first decade.

6. The persistence of migraine symptoms up until and through the sixth decade is not uncommon.

7. Migraine patients are usually above the average both mentally and physically.

8. Treatment should consist of thorough elimination of the foods and dusts to which the patient is found specifically sensitive.

9. Results in the treatment of migraine are as good or better than those obtained in nearly any other chronic disease.

REFERENCES.

1. Vaughan, Warren T.: Allergic Migraine, J. Am. Med. Assn., 1927, 88, 1383.
2. Balyeat, Ray M.: The Hereditary Factor in Allergic Diseases, with Special Reference to the General Health and Mental Activity of Allergic Patients, AM. J. MED. SCI., 1928, 176, 332.

MULTIPLE ANEURYSMS OF THE ARTERIES OF THE RIGHT ARM ASSOCIATED WITH ARTERIOVENOUS FISTULA AND ARTERIAL EMBOLISM.

REPORT OF A CASE.*

By DWIGHT L. WILBUR, M.D.,

FELLOW IN MEDICINE, THE MAYO FOUNDATION,
ROCHESTER, MINN.

THE association of multiple arterial aneurysms in an extremity with arteriovenous fistula and arterial embolism is rare. The case herein reported is of a patient who presented aneurysms of the brachial, radial, superficial palmar, common volar digital and volar digital arteries of the right arm, and also embolism of the radial

* Work done under the direction of Dr. G. E. Brown, Division of Medicine, The Mayo Clinic.

artery and an arteriovenous fistula of the hand. The interest in such a combination of changes is no less intense from a pathologic standpoint than that aroused clinically because of the wide range of physiologic studies possible. Of equal interest are the therapeutic problems raised by such a group of anomalies.

Aneurysms of the arteries of the upper extremities are uncommon and usually traumatic in origin. Holt, in a review of the literature up to 1882, found only 14 cases of brachial aneurysm due to disease. Lyle, in 1924, in an exhaustive review of the literature, was able to collect data on 61 published cases of aneurysms of the palmar arches and added one case of his own. Of these, 2 cases only were spontaneous; the remainder were chiefly traumatic in origin and therefore affecting the superficial palmar arch (54 cases) more frequently than the deep arch. Pemberton, in a review of the cases in which an aneurysm was treated surgically in The Mayo Clinic from January, 1915, to April, 1926, reported a total of 41 cases of arterial and arteriovenous aneurysm. Twenty-five of these were arteriovenous, 16 were acquired, and 9 were congenital. Reid,¹⁶ in a study of 33 cases of arteriovenous fistula, disclosed two present in the hand. These were both the result of trauma. He included in this group 6 congenital cases which were chiefly of the cirroid aneurysm type. The small number reported indicates that the lesions are rare.

From the pathologic standpoint, the etiology of such aneurysms in the absence of trauma and syphilis and the development of congenital arteriovenous communications is interesting. Multiple aneurysms may develop in different arteries of the body, as in the case recorded by Kolodny, in which there were aneurysms of the right popliteal, right axillary, left carotid, right external iliac arteries and the descending thoracic aorta. On the other hand, they may be multiple and localized to one peripheral vessel, such as in the case reported by Skillern, in which there were two small aneurysms in the brachial artery. It is well known, of course, that multiple aneurysms of the aorta and cerebral vessels are not uncommon. It is interesting to speculate whether or not multiple aneurysms in one vessel may be due to the effects of trauma or to other influences on an artery which already constitutes a place of lowered resistance. The question of the exact mode of development of arteriovenous fistula, cirroid aneurysm and other abnormal arteriovenous communications is still unsettled. The belief at present is that these communications are either developmental anomalies in which capillaries are not formed so that the artery and vein communicate directly, or that they are neoplastic in origin.

Physiologic studies of arteriovenous fistulas are unusually interesting from the standpoint of the local and general effects produced. Among the former may be included changes in surface temperature of the affected part, the marked development of neighboring col-

lateral circulation, the changes in the length of the extremity in certain cases, and dilatation of the proximal artery and the veins. Brown and Pemberton called attention to the high oxygen content of the blood of the regional veins and to its pathognomonic significance in the diagnosis of arteriovenous fistula. The general effects on the cardiovascular system have been particularly emphasized by Holman. As he has pointed out, the changes produced depend primarily on the size of the fistula and on an unobstructed return flow to the heart. The changes produced include lowering of systemic blood pressure, elevation of pulse rate, increase in blood volume, and dilatation and hypertrophy of the heart, besides other changes.

TABLE I.—MEASUREMENTS OF LENGTH AND CIRCUMFERENCE OF BOTH ARMS.

	Right, cm.	Left, cm.
Circumference:		
Midarm above aneurysm	23.7	23.7
Level of aneurysm	26.4	22.7
Midforearm	24.0	24.7
Wrist	16.5	16.0
Base of index finger	9.5	8.0
Length:		
Distal end of clavicle to tip of middle finger	84.5	81.0
Tip of olecranon to tip of middle finger	52.0	49.0
Distal crease of wrist to tip of middle finger	19.0	19.0

Because of the great interest which the following case aroused clinically and because of the physiologic and pathologic studies made, it was considered to be worth reporting.

Report of Case. The patient, a farmer, aged forty-three years, registered at the Clinic February 13, 1929, for treatment of an aneurysm of the right brachial artery which had developed gradually over a period of fourteen years without apparent cause. The past medical history was essentially negative and the patient denied syphilitic infection. The right arm was not disabled until December, 1928, when he experienced a sudden sharp agonizing pain just above the wrist in the right radial artery. The hand became blue and numb and morphine was required to relieve the pain. Since that time the right index finger and the surrounding palm had been somewhat blue and after careful questioning the patient remembered that he had always had a "hot spot" in the palm at the base of the index finger.

The general examination was essentially negative with the exception of the right arm. There was an expansile pulsating mass, approximately 5 cm. in diameter, just above the internal condyle of the humerus. The superficial veins of the forearm were distended and there was a soft swelling 2 cm. in diameter over the radial artery in the middle portion of the forearm. The pulsations of the radial artery were vigorous up to the wrist, where they suddenly ceased, and at this point the artery was exceedingly tender. The palm at the base of the index finger was cyanotic, spongy and soft, as was the index finger up to the proximal interphalangeal joint. The right forearm was 3 cm. longer than the left. Abnormal auscultatory sounds were not present. Significant changes in blood pressure in the right arm were absent and venous pressure was roughly equal in both forearms. Laboratory examinations were negative. A roentgenogram of the right hand was reported as showing an old fracture of the first phalanx of the fifth finger.

Special examinations disclosed definitely abnormal responses to changes in posture on the right with blanching of the fingers on elevation of the arm (180°), quick filling of the index finger and surrounding palm (purple) and slow filling of the remainder of the hand which remained pink with the arm at the side (0°). Compression of the palm at the base of the right index finger, which presumably obliterated the arteriovenous fistula, caused the pulse beat to drop almost immediately five to seven points on several occasions^{8,12}. On fluoroscopic examination, it was found that the heart was of normal size and there was no change in size with postural changes of the right arm or obliteration of the fistula. On compression of the brachial



FIG. 1.—Right and left arms before operation; just above the right elbow is the swelling produced by the brachial aneurysm; the superficial veins on the right are more prominent, especially on the radial side; the fingers on the right are drawn toward the ulnar side.

artery above the aneurysm, color in the hand returned in two to three minutes; normally it would return almost immediately. The results of oxygen and temperature studies are shown in Tables II and III. Calorimetric studies of the hands preoperatively showed that elimination of heat in small calories in twenty minutes for the entire hand was, for the right hand, 260, and for the left, 130 (normal 110 to 130).

It was obvious that the patient had a right brachial aneurysm and an arteriovenous fistula of the right hand, as indicated by the warmth of the hand, the neighboring engorged veins, the calorimetric studies and the presence of almost pure arterial blood in the regional veins of the right hand.

Following adequate development of the collateral circulation of the right arm by the method advocated by Matas, the brachial aneurysm was surgically obliterated March 12, 1929, although it was realized that the presence of the arteriovenous fistula was a serious complicating factor. Return flow from the distal end of the brachial artery following ligation of the proximal end was satisfactory at the time of operation. Following operation, there was considerable pain in the right hand, which was partially relieved by the application of heat. Gradually the pain became more severe and the impression was gained that thrombosis of some of the vessels of the hand had occurred. Typhoid vaccine and radium chlorid intravenously¹ and heat were of no benefit in relieving the steady burning pain. The hand was



FIG. 2.—Right and left arm before operation; volar surface.

blue and cold except for the "hot spot" which was still warm, and motion was very much limited. It was obvious that the arterial blood supply to the hand was inadequate, but it did not seem wise to attack the arteriovenous fistula surgically because experience in previous similar cases had shown this to be a difficult, if not impossible, procedure to carry out successfully. It was finally necessary to amputate the forearm to relieve the pain. The patient's convalescence was uneventful.

The arterial system was injected with mercury (Horton's method). The course followed by the mercury can be seen in roentgenograms taken during various stages of the injection (Fig. 3). The mercury, under low pressure, entering the radial artery with the arm in the horizontal position passed through small anastomosing branches to the volar interosseous artery and

then on to the larger arteries of the palm. Within a few minutes the mercury was returning from a superficial branch of the cephalic vein. Fig. 3a shows that at this time none of the arteries of the fingers was filled with mercury, and the mercury was already returning from the vein. Slight increase in pressure produced injection of the vessels about the base of the index finger (Fig. 3b), but still mercury did not enter the finger tips. With further slight increase in pressure, the mercury finally entered the arteries of the fingers but it also filled most of the venous system of the hand (Fig. 3c).

TABLE II.—VENOUS OXYGEN STUDIES OF RIGHT HAND.

Blood.	Date.	Oxygen capacity, vol. per cent for each 100 cc.	Oxygen content, vol. per cent for each 100 cc.	Saturation, per cent.	Unsaturated blood, vol. per cent.	Unsaturated, per cent.
Vein of right arm near wrist	Feb. 18, 1929	17.7	15.6	88.2	2.08	11.8
Vein of right index finger	Mar. 30, 1929	18.5	17.0	91.0	1.50	9.0
Control vein of left arm	Mar. 30, 1929	..	12.5	52.0		
Normal arterial	21.0	20.0	95.0	1.00	5.0
Venous	21.0	14.0	70.0	7.00	30.0

TABLE III.—SURFACE TEMPERATURE STUDIES OF RIGHT AND LEFT HANDS: BEFORE AND AFTER OPERATION, DEGREES CENTIGRADE.

Four Weeks Before Operation.

Site.	Right.		Left.	
	Tip.	Second joint.	Tip.	Second joint.
Thumb (2 and 3)*	27.2	28.7	28.6	30.3
First finger (5 and 6)	28.6	30.6	27.7	29.5
Second finger (7 and 8)	25.4	30.5	28.4	29.4
Third finger (9 and 10)	25.7	29.1	29.3	29.7
Fourth finger (11 and 12)	25.1	28.2	29.6	29.5
Palm (4)		32.1		29.4
Palm (13)		29.4		29.4
Palm (15)		32.6		30.2
Arms		30.9		30.9

Two Weeks After Operation.

Site.	Right.	Left.
Palm (2)*	30.6	30.9
(15)	31.5	30.9
(14)	30.1	31.0
(4)	35.0	
Fingers (5)	31.4	
(6)	30.0	
(7)	28.6	31.2
(11)	28.5	30.3

Three and a Half Weeks After Operation.

Site.	Right.	Left.
Fingers (11)*	33.3	36.6
(9)	33.3	36.5
(7)	33.7	36.3
(6)	35.7	36.9
	34.9	36.0
Distal palm (12)	36.4	37.2
(10)	36.9	37.2
(8)	35.0	36.3
(4)	34.0	36.3
(2)	37.0	36.4
Palm (1)	37.5	37.5
(15)	36.5	36.5
(13)	35.8	36.1
(14)	37.0	36.3

* Numbers refer to points on hand shown in Fig. 4.

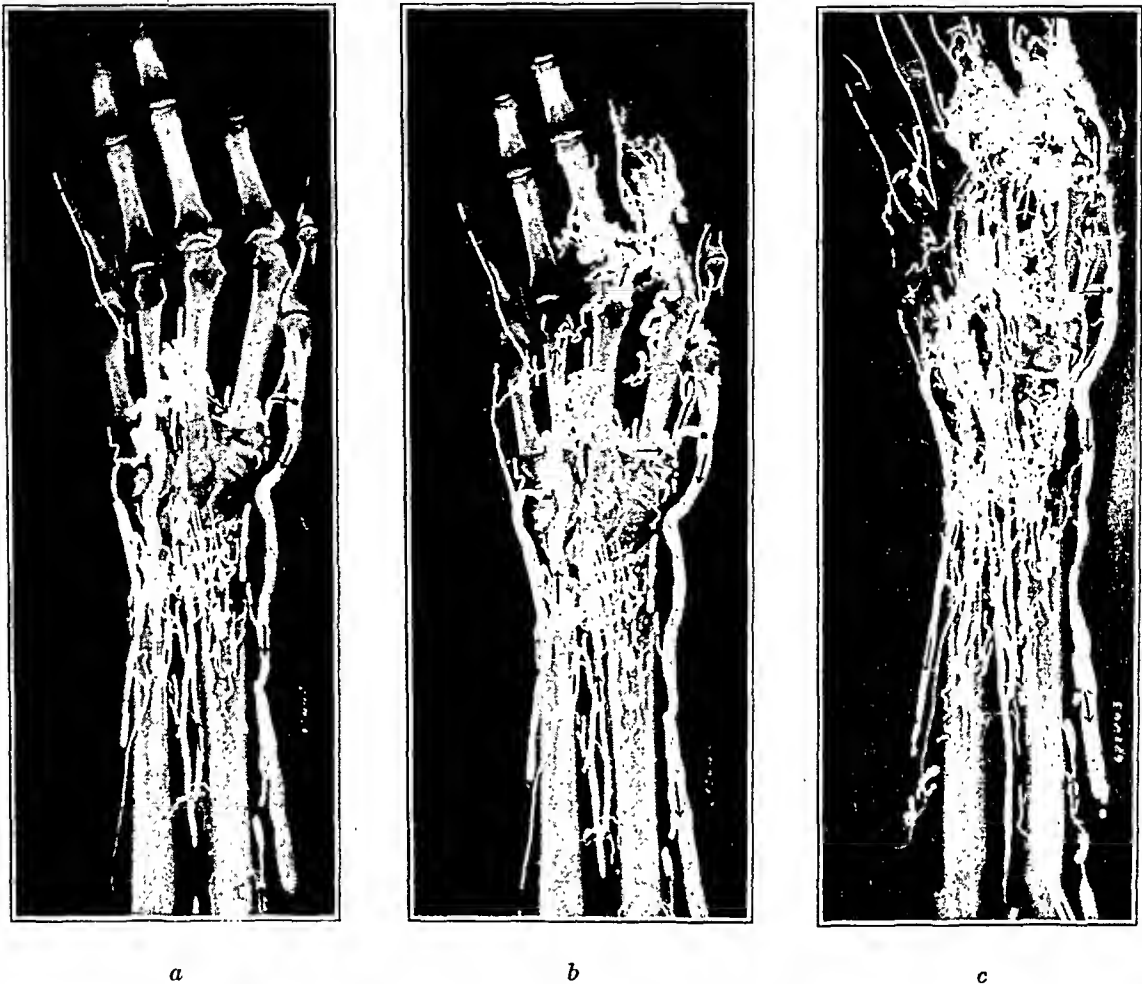


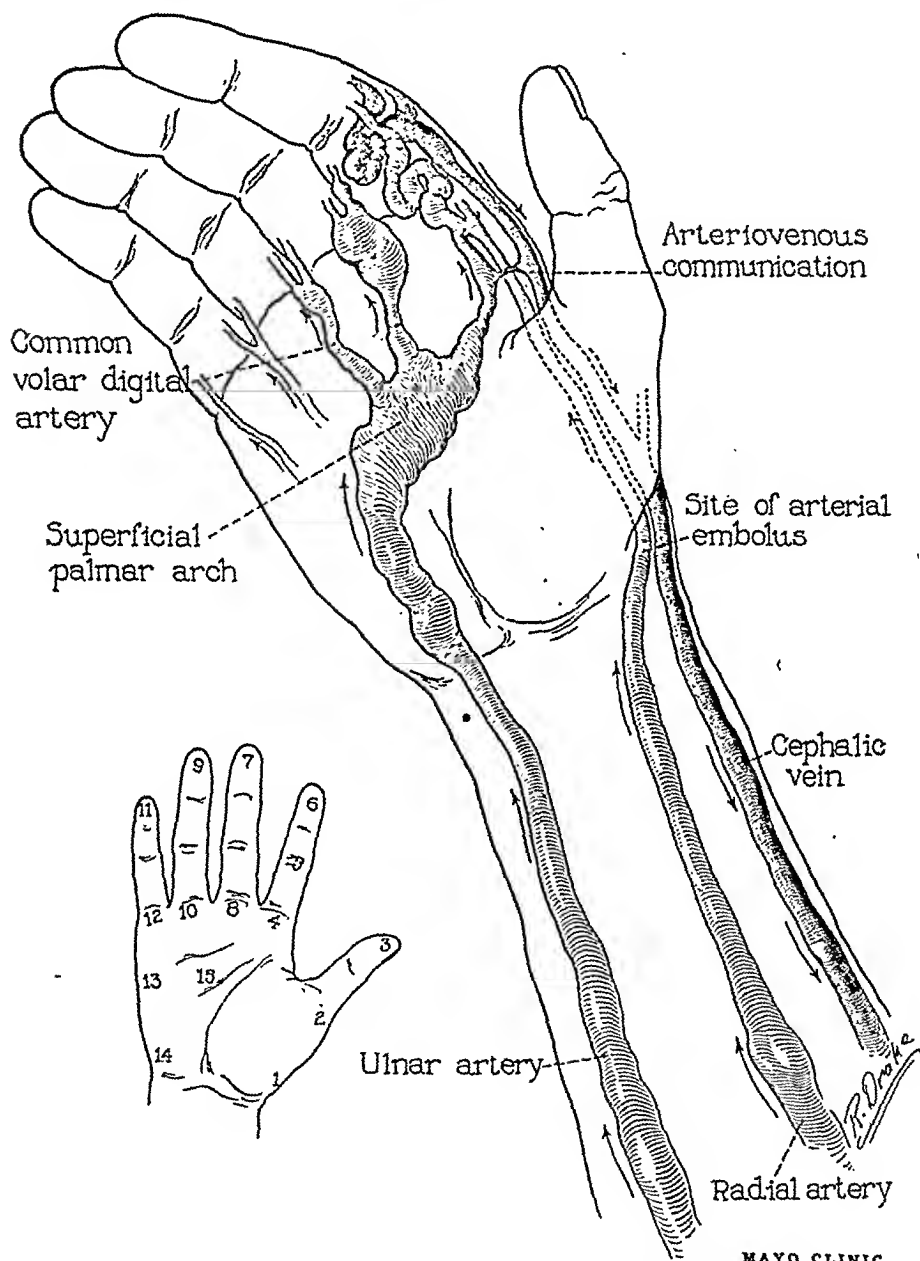
FIG. 3.—The vascular tree of the right forearm during injection with mercury following amputation (Horton's technique). The arrows indicate the direction of flow. The large shadow on the right is a superficial branch of the cephalic vein.

a.—Low pressure. Mercury was allowed to flow in the radial artery in the middle portion of the forearm (as shown by the arrow at bottom of photograph). It is obstructed after a short distance because of thrombosis in the vessel, and therefore, passes through small arteries over the radius to enter the volar interosseous artery (lying between the radius and ulna). Proceeding to the palm, it enters the palmar arteries and flows toward the base of the second metacarpal bone. It then passes into a superficial branch of the cephalic vein near the point indicated by the arrow and dot, and returns by the vein toward the heart.

b.—Slightly higher pressure than *a*. Flow the same as in *a*, but in addition the mercury fills the aneurysms and dilated vessels in the region of the proximal phalanges of the index and middle fingers; it may be noted that the arteries of the last three fingers are not filled with mercury.

c.—Slightly higher pressure than *b*. Flow same as in *b*; in addition, the mercury has finally entered the vessels of the fingers but at the same time nearly all of the venous channels contain mercury as well; the constancy of the communication at the site of the arrow and dot and the absence of mercury in the course of the radial artery may be noted.

Anatomic study of the vessels revealed small aneurysms of the radial, superficial, palmar, common volar digital and volar digital arteries, nearly all of which contained adherent and organized thrombi (Fig. 4). The radial



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FIG. 4.—Large vessels of the right hand as determined by dissection. The chief points of interest are: (1) Dilatation of the radial and ulnar arteries; (2) small aneurysm of the radial artery; (3) narrowing of radial artery at site of embolism; (4) aneurysmal dilatation of the superficial palmar arch with absence of volar branches to the last two fingers; (5) aneurysm of the common volar digital artery to the index and middle fingers with aneurysm of the volar digital artery to the index finger; (6) tortuous veins surrounding base of index finger; (7) probable site of arteriovenous fistula; (8) prominent superficial cephalic vein.

artery above the wrist was dilated and tortuous, and at the wrist it was unusually small and completely obliterated. The superficial veins were dilated, especially those on the radial side of the forearm. A definite

arteriovenous communication was not found in careful dissection of the forearm and hand. A diagram of the condition in the vascular tree following dissection of the forearm is shown in Fig. 4.

The arterial walls throughout the forearm were abnormally sclerotic and presented fibrotic changes of the media and marked but irregular proliferation of the intima with excessive thinning in the areas of aneurysmal dilatation. The majority of the vessels contained organizing thrombi. There was slight evidence of an inflammatory process as indicated by perivascular lymphocytic collections. The veins carrying the arterial blood presented histologic pictures somewhat similar to those of arteries with hypertrophy of the elastic and muscular portions of the walls of these veins.

Comment. The cause of such extensive vascular disease of an extremity is uncertain. The absence of evidence of syphilis practically excludes this factor. The presence of a moderate number of perivascular lymphocytic collections and other histologic features in several of the sections was not inconsistent with the diagnosis of thrombo-angiitis obliterans, although not pathognomonic of this disease. It is possible, as suggested by Skillern, that aneurysms of this type are the result of some abnormal influence on arteries already a place of lessened resistance, or that the aneurysms developed in the arteries proximal to an arteriovenous fistula, as has been reported by Curtis, Osler and Da Costa. The absence of general systemic effects of the fistula make this seem unlikely. The conclusion is evident that the arterial changes were due to some defect in arterial development or to some abnormal sclerotic process in the walls of the vessels, although an infectious process cannot be absolutely excluded. The etiology of the arteriovenous fistula is uncertain also but several factors point to it as being congenital, that is, the history of a hot spot in the palm of the hand throughout life, the history of slow healing of a fractured phalanx ten years previously and the excessive length of the right forearm which must have occurred prior to the age of twenty years.

Anatomic preoperative studies showed the right forearm to be 3 cm. longer than the left. This is a common observation in the presence of an arteriovenous fistula before complete skeletal ossification has occurred and is the result of the presence of excessive arterial blood at the epiphyses. It seems probable that the arteriovenous fistula was in the palm somewhere near the base of the index finger (Fig. 4). This is borne out by the discoloration in this area, the bradycardia response to pressure over this point, and the escape of mercury into the veins in this region (Fig. 3), at low pressure during the injection by Horton's method following amputation. The fistula was evidently small and probably contained multiple openings. The microscopic data are significant in that the vessels showed a markedly abnormal sclerotic process, the exact nature of which is not certain. An infectious process could not be absolutely excluded. The thrombi present in the majority of the arteries appeared to be of approximately the same age.

It is interesting to confirm the changes previously found by others in a vein performing some arterial functions. Reid,¹⁵ in a microscopic study of the regional vessels following experimentally produced arteriovenous fistula, found hypertrophy of the walls of the proximal veins and an increase in the elastic tissue as a result of the assumption of arterial function by the vein. In the present study definite changes were found in the veins, giving them the general histologic appearance of arteries. This would indicate an increase in the venous pressure in these vessels but this was not observed clinically with the crude method used for its determination. It is a question whether changes in the histologic appearance of a vein would occur in the presence of an abnormally high content of oxygen of the venous blood alone, or if such changes depend entirely on the increase in pressure and volume of the blood in the regional veins as a result of an arteriovenous fistula.

The physiologic changes present were of interest chiefly because of the local effects produced and in all probability were due largely to the arteriovenous fistula. General circulatory effects were absent excepting that bradycardia was produced by compression of the fistula. Although the collateral circulation of the upper part of the arm was poorly developed and required further development before operation, the collateral circulation surrounding the arteriovenous fistula was well developed, as indicated by the observation by mercury injections. This accords with Reid's¹⁷ clinical and experimental data that arteriovenous fistula is the most powerful stimulus there is to the development of collateral circulation of the surrounding vessels. The oxygen content of the blood of the regional veins was almost that of pure arterial blood and, as Pemberton and Brown have indicated, is absolute proof of the existence of an abnormal arteriovenous communication.

Calorimetric and surface temperature studies revealed the expected increase in production of heat by the right hand. The excess of arterial blood passing through it was sufficient almost to double the calorimetric output of this extremity over the left. There was a slight increase in surface temperature of the right hand in the area at the base of the index finger. Elsewhere it was considerably colder than the left.

A better understanding of the clinical problems presented by this case is obtained from the pathologic study made. It was obvious that the brachial aneurysm should be attacked surgically but the presence of the arteriovenous fistula increased the hazard greatly for such an attack. It was more than a problem of simply developing the collateral circulation of the arm as a whole to the point of caring for the tissues following obliteration of the brachial artery. It did not seem justifiable, in view of experience in other cases, to attack the arteriovenous fistula directly. Following operation the patient had a great deal of pain in the right hand, the cause of which

was not quite certain at the time. Attempts were made to increase the circulation to the hand by the use of heat locally and typhoid vaccine intravenously, but without success. Thrombosis of the arteries (superficial palmar, radial and ulnar) had occurred and the small amount of arterial blood entering through the collateral channels was being shunted through the fistula before it could get to the fingers. This was well demonstrated by the injection of mercury into the arterial tree following amputation. Before the mercury, under low pressure, had entered any of the vessels of the fingers it had passed into the venous tree. Horton¹ in his studies has found that the normal arterial tree will hold mercury up to a pressure of 75 to 90 mm. of mercury, and in some cases as high as 120 to 150 mm. The injection of the vascular tree in the case presented was carried out at a pressure of less than 10 mm. The venous tree in the normal state, therefore, rarely contains mercury as it does not readily pass through the capillaries at low pressures. These data are added proof of the existence of the arteriovenous fistula, and are of interest clinically in showing that flow through an arteriovenous fistula is accomplished at a much lower pressure than is required for normal flow through a capillary bed.

The pain was undoubtedly due in large part to the thrombosis of the vessels and possibly also to the anemia of the tissues, if the latter will produce pain. It did not seem justifiable to approach the arteriovenous fistula surgically, and as the fistula could not be found anatomically following amputation this judgment proved sound. The only course remaining was amputation, which was carried out without incident.

It does not seem possible, in the light of the anatomic changes, that a better result could have been obtained. The presence of the smaller aneurysms of the radial, superficial palmar and digital arteries was probably without significance clinically although of great interest pathologically.

Summary. The association of multiple aneurysms of the right brachial, radial superficial palmar, common volar digital and volar digital arteries with an embolus in the radial artery and an arteriovenous fistula of the hand is recorded. This combination of changes is of unusual interest to the physician because of its rarity and the many fields that open for investigation, and to the surgeon because of the many difficult therapeutic problems it presents.

BIBLIOGRAPHY.

1. Allen, E. V., and Brown, G. E.: *Thrombo-angiitis Obliterans: A Clinical Study of 200 Cases: II. Treatment and Prognosis*, *Ann. Int. Med.*, 1928, 50, 550.
2. Brown, G. E.: *Abnormal Arteriovenous Communications Diagnosed from the Oxygen Content of the Blood of Regional Veins*, *Arch. Surg.*, 1929, 18, 807.
3. Curtis, B. F.: *The Treatment of Arteriovenous Aneurysm, with Two Cases Treated by Extirpation*, *AM. J. MED. SCI.*, 1891, 101, 142.
4. Da Costa, J. C.: *Operation for Varicose Aneurysm of the Brachial Artery*, *St. Paul Med. J.*, 1914, 16, 310.

5. Holman, E.: Arteriovenous Aneurysm, Calif. and West. Med., 1929, 30, 307.
6. Holt, L. E.: True Aneurysm of the Brachial Artery at Its Upper Third Cured by Compression Maintained for Ten Hours by Means of a Conical Pad, with a Résumé of the Literature on the Subject, AM. J. MED. SCI., 1882, 83, 382.
7. Horton, B. T.: A Study of the Vessels of the Extremities by the Injection of Mercury. Surg. Clin. North America, 1930, 10, 159.
8. Israël, J.: Angiectasis im Stromgebiete der A. tibialis antica: Beobachtung einiger bemerkenswerter Phaenomene nach Unterbindung der A. femoralis, Arch. f. klin. Chir., 1877, 21, 109.
9. Kolodny, A.: Multiple Aneurysms of Large Vessels: Report of a Case, J. Am. Med. Assn., 1926, 86, 397.
10. Lyle, H. M.: Aneurysm of the Palmar Arches, Ann. Surg., 1924, 80, 347.
11. Matas, R.: Arteriovenous Fistula of the Femoral Vessels (Aneurysmal Varix) on a Level with the Origin of the Profunda, Surg. Clin. North America, 1922, 2, 1165.
12. Nicoladoni, C.: Phlebarteriectasie der rechten oberen Extremität, Arch. f. klin. Chir., 1875, 18, 252.
13. Osler, W.: A Case of Arteriovenous Aneurysm, Bull. Johns Hopkins Hosp., 1905, 16, 146.
14. Pemberton, J. deJ.: Arteriovenous Aneurysm, Arch. Surg., 1928, 16, 469.
15. Reid, M. R.: The Effect of Arteriovenous Fistula Upon the Heart and Blood-vessels: An Experimental and Clinical Study, Bull. Johns Hopkins Hosp., 1920, 31, 43.
16. Reid, M. R.: Studies on Abnormal Arteriovenous Communications, Acquired and Congenital: I. Report of a Series of Cases, Arch. Surg., 1925, 10, 601.
17. Reid, M. R.: Abnormal Arteriovenous Communications Acquired and Congenital: III. The Effects of Abnormal Arteriovenous Communications on the Heart, Bloodvessels and Other Structures, Arch. Surg., 1925, 11, 25.
18. Skillern, P. G., Jr.: Arteriectasis of the Brachial Artery, Internat. Clin., 1913, 4, 237.

LEUKOPENIA RESEMBLING AGRANULOCYTOSIS WITH RECOVERY.

BY WILLIAM P. THOMPSON, M.D.,

ASSISTANT PHYSICIAN, PRESBYTERIAN HOSPITAL, NEW YORK CITY.

(From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.)

SINCE the description of agranulocytic angina in 1922 by Schultz several clinical reports have appeared illustrating the association of the agranulocytic type of blood picture with various other conditions. Among the most recent is the case of almost complete agranulocytosis associated with sepsis presented by Blumer.¹ Another is the group collected by Farley² of 7 cases of depressed bone-marrow function following arsphenamin therapy. A fatal outcome has been the almost universal rule in the typical agranulocytic angina cases, as well as in most of the described variations.

During the past year there have been a number of cases in the wards of the Presbyterian Hospital that approached the agranulocytic type of blood picture, associated with throat infection, but in which recovery took place.

These cases have been so similar in their symptoms, physical signs, and blood picture that they are briefly presented as another variant

in the group of infections associated with depression of the polymorphonuclear leukocytic elements of the blood.

The clinical picture consists of:

1. Several days of fever, slowly rising and swinging, often reaching 103° to 104° F. This fever is associated with no symptoms other than mild chilly sensations, and there are no abnormal physical findings.

2. After several days of the fever, there appear moderately enlarged, soft, tender lymph nodes and spleen.

3. Coincident with the enlargement of the lymph nodes and spleen there is a change in the white blood count with a moderate to an extreme leukopenia and reduction in the polymorphonuclear leukocytes, often reaching an almost complete agranulocytosis. There is a relative increase in the mononuclear cells and abnormal forms are sometimes seen.

4. After the appearance of the lymph nodes and well toward the end of the disease, the pharynx becomes red and sore and on the posterior pharyngeal wall may be seen scattered, round, superficial, whitish spots looking, on the red background, very like *Staphylococcus albus* colonies on a blood-agar plate.

The disease lasts from one to three weeks and, with but one possible exception, all of the cases have recovered promptly and completely, almost by crisis. The syndrome is somewhat similar to, but not identical with, the disease known as infectious mononucleosis or glandular fever.

Case Reports. CASE I.—P. V. (Unit No. 85617), an Italian contractor, aged sixty-nine years, came into the wards complaining of pain in the stomach and loss of weight of six months duration. This was subsequently found, at operation, to be caused by a large inoperable carcinoma.

His blood count on admission was normal: 5,000,000 red cells, 10,000 white blood cells, 83 per cent polymorphonuclears, 17 per cent lymphocytes. For three weeks he was without new symptoms and his temperature was persistently normal. Quite unexpectedly, at the beginning of the fourth week in the hospital, his temperature jumped to 102.4°. The only symptom was mild, scattered pains in the joints. Blood cultures on this day and on the two succeeding days were sterile. The course of his temperature and his blood count is shown in the chart on page 234. On the third day of this acute illness, there was moderate, diffuse reddening of the throat, insufficient to cause symptoms. On the following day, cervical and axillary lymph nodes were noted as being definitely enlarged, soft, and tender. The tip of the spleen appeared below the costal margin. With the high temperature, relatively low pulse rate, lack of symptoms, palpable spleen, and leukopenia, a tentative diagnosis of typhoid fever was made. On the fifth day of this acute illness his throat became sore, and round, superficial, white spots appeared in the pharynx, resembling *Staphylococcus albus* colonies on a blood plate. At the end of the week the temperature had returned to normal, the symptoms had entirely disappeared, the spleen and lymph nodes had reduced in size, and the acute illness was over. Subsequent blood counts were perfectly normal except for a slight progressive secondary anemia presumably associated with the carcinoma.

P.V

85617

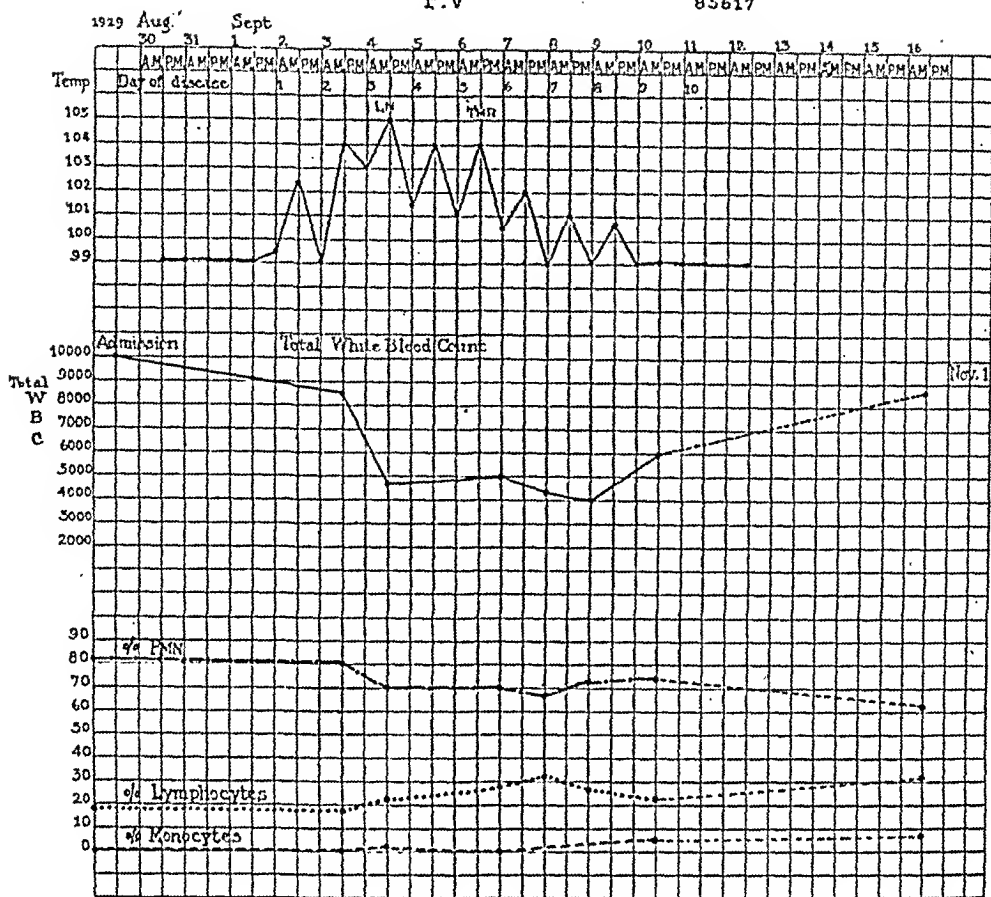


CHART I.—LN, appearance of enlarged lymph nodes. THR, appearance of pharyngitis.

B.F.

230689

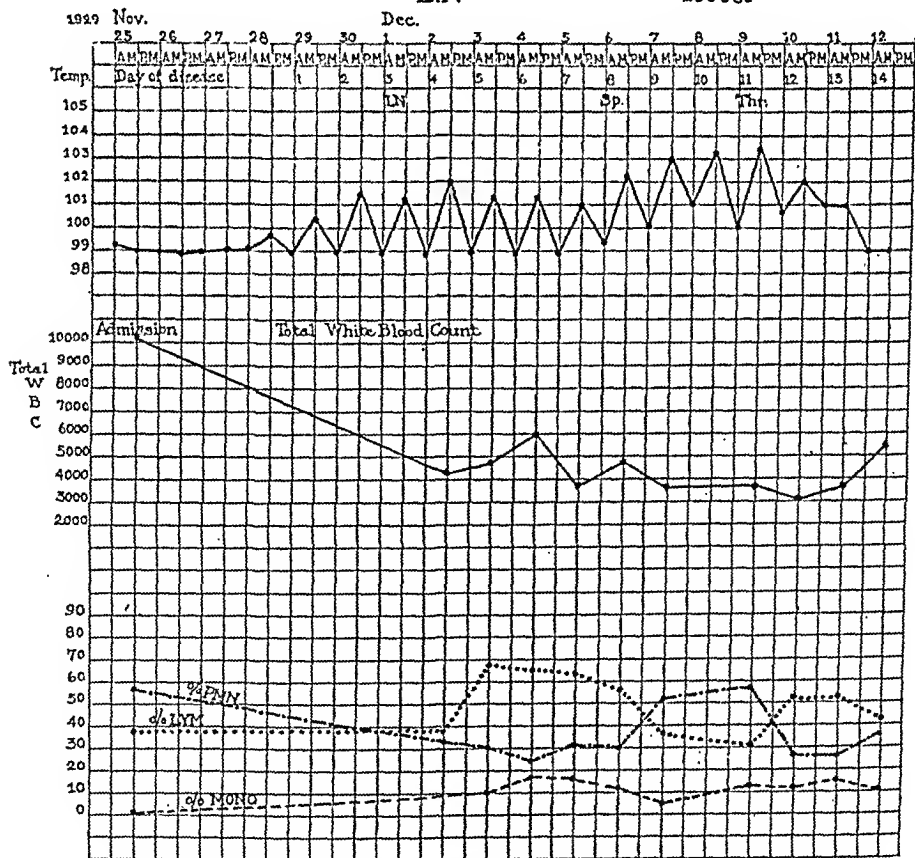


CHART II.—LN, appearance of enlarged lymph nodes. Sp, appearance of spleen; Thr, appearance of pharyngitis.

CASE II.—B. F. (Unit No. 230689), a Jewish subway guard, aged forty years, was admitted to the medical wards as a possible mild exophthalmic goiter. His admission blood count showed 4,700,000 blood cells, 10,300 white blood cells, 56 per cent polymorphonuclears, 37 per cent lymphocytes; no abnormal cells were seen. For the first three days his temperature remained normal. On the fourth day it began to be progressively elevated. The temperature course throughout this acute illness, together with the white blood count, is shown on the chart on page 234. There were no symptoms with the initial rise in temperature and no physical signs to explain it other than a very slightly reddened throat which had been noted several times in the medical dispensary during the two months he was followed there before admission. A blood culture showed no growth. After a week of this unexplained fever, moderate enlargement of the posterior cervical lymph nodes was noted. On the tenth day of this acute illness, the patient was still without symptoms and there was no change in the appearance of the throat. The glands were thought to be even larger and were described as soft and slightly tender. The tip of the spleen could just be felt on deep inspiration. It was not until the twelfth day that his throat was noticed as being more diffusely reddened than previously, and on the day following, small, white, round, superficial ulcerations, resembling *Staphylococcus albus* colonies on a blood plate, were seen. With the appearance of these, the temperature began falling, reaching normal on the sixteenth day. This was followed by rapid clearing of the throat lesions, prompt regression of the lymph nodes, and a rapid return of the blood count to normal.

These two cases show the complete course of the disease, with an afebrile period before and after.

CASE III.—G. R. S. (Unit No. 85565), a graduate nurse, aged thirty-six years, came into the medical wards with a two and a half week history of chills, fever and scattered, variable aches and pains.

On admission her temperature was 104.6° and she seemed acutely ill. Physical examination revealed slight cyanosis, flushed face, and enlarged, nontender cervical and axillary lymph nodes. The spleen was just palpable, soft, and not tender. The remainder of the examination was negative. The throat was not sore or inflamed. Her admission blood count showed normal red count and hemoglobin. White blood cells numbered 2500, 56 per cent polymorphonuclears, and 44 per cent lymphocytes, with no abnormal cells. On the day after admission, her throat for the first time became sore with the appearance of diffuse redness and scattered, round, white, superficial ulcerations, resembling *Staphylococcus albus* colonies on a blood plate. The day after admission her highest temperature was 103.6°. The lymph nodes and spleen appeared slightly larger. The leukopenia persisted and 6 per cent of abnormal white cells had made their appearance. Two blood cultures were sterile. It was felt by those who saw her at this time that she was probably developing an acute leukemia. On the third day after admission, her temperature spiked again to 103.2°. At this time there were 4600 white blood cells, 56 per cent polymorphonuclears, 22 per cent myelocytes, and 5 per cent myeloblasts. Her temperature fell practically by crisis on the fourth day, three weeks after the onset of symptoms, and remained normal. Her symptoms rapidly disappeared with a return of the blood count to normal and a regression in the size of the lymph nodes and spleen. She was discharged on the eighth day after admission for further convalescence.

She died suddenly four days after discharge with symptoms suggesting occlusion of a cerebral artery. Autopsy was not obtained.

CASE IV.—S. W. (Unit No. 224143), a student nurse, aged eighteen years, was admitted with a five-day history of headache and general malaise. During these five days, physical examination was entirely negative, the highest temperature being 101.8°. On the fifth day of her illness, previously palpable cervical lymph nodes were thought to have enlarged and become tender. During the five days before admission, she had not complained of sore throat and examination was negative.

Examination at the time of admission revealed a moderately ill young woman with a temperature of 102.6°. The throat was negative. There was moderate enlargement of the cervical lymph nodes, which were soft and tender. The tip of the spleen was just palpable. Her blood count on admission showed 4000 white blood cells, 30 per cent polymorphonuclears, 61 per cent small lymphocytes, and 9 per cent monocytes. The red count was normal and no unusual white cells were seen. No blood culture was taken. Her temperature ranged between 100° and 102°, tending downward. On the tenth day of her disease, there appeared a diffuse reddening of her throat, with scattered, round, whitish spots, resembling *Staphylococcus albus* colonies on a blood plate. The white blood cells on this day numbered 7000, 24 per cent polymorphonuclears, 66 per cent lymphocytes, and 7 per cent monocytes. The lymphocytes were rather large and suggested slightly immature forms. Her temperature reached normal on the fourteenth day of her disease and she was discharged on the sixteenth day for further convalescence. Her blood count at the time of discharge was as follows: white blood cells 12,500, polymorphonuclears 32 per cent, and lymphocytes 66 per cent.

She returned to work after two weeks convalescence without symptoms or abnormal physical signs and with a normal blood count and differential.

CASE V.—G. M. (Unit No. 74475), an American salesman, aged twenty-three years, entered the hospital with a three-day complaint of scattered aches and pains, mild chilly sensations, and fever. The admission diagnosis was "grippe."

Examination revealed a well-developed and well-nourished young man looking acutely ill. His throat was slightly injected and the cervical lymph nodes were moderately enlarged. The temperature curve and the white blood count are shown in the chart on page 237. During the second week of his stay in the hospital, there was considerable further increase in the size of the cervical lymph nodes, together with moderate enlargement of the axillary and inguinal nodes and spleen. At this time several whitish spots were observed on the posterior pharyngeal wall suggesting *Staphylococcus albus* colonies on a blood plate. These disappeared promptly after the return of temperature to normal. Two blood cultures taken during the febrile stage were negative.

He was seen in the medical follow-up four months after discharge from the wards, at which time he was without symptoms or physical signs of any kind.

Case V is the only one of the group that did not have a severe leukopenia during the entire illness. This case more than any of the others suggests the syndrome known as glandular fever. This diagnosis was seriously considered during the patient's stay in the wards, but it was felt by most of those who saw him that the clinical picture was not quite typical of that disease as it has been described in the literature and as it has been seen in this hospital.

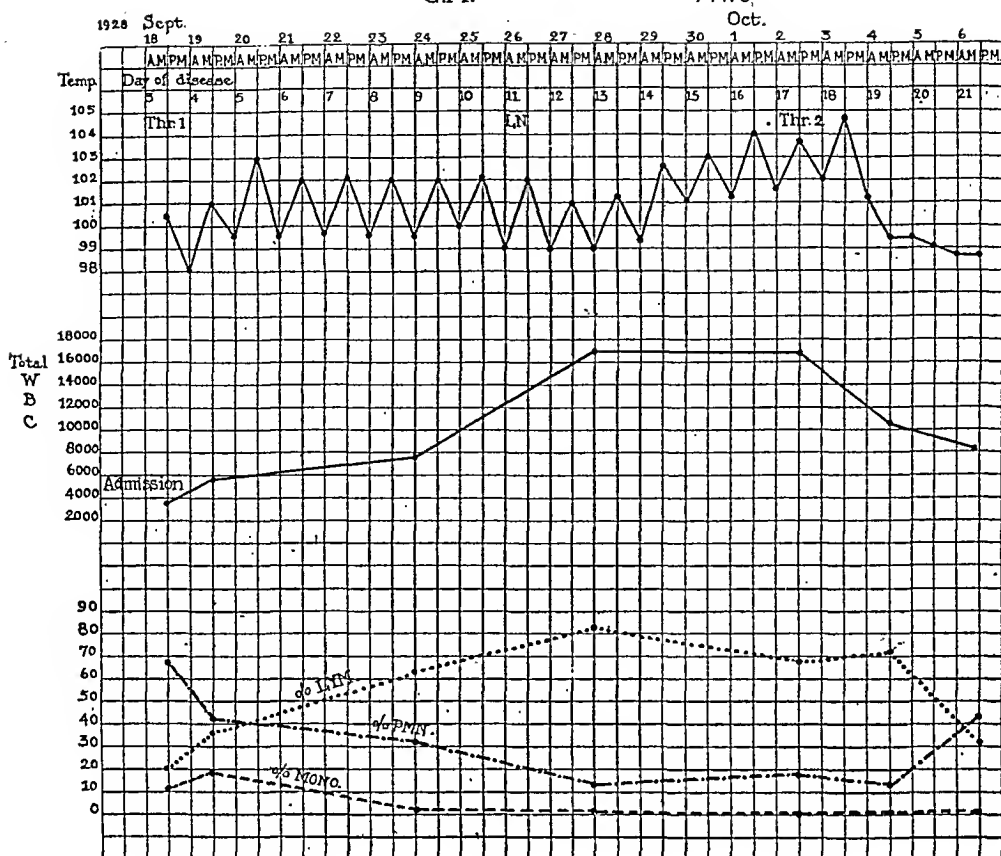


CHART III.—LN, appearance of enlarged lymph nodes. Thr. appearance of pharyngitis.

E.A.

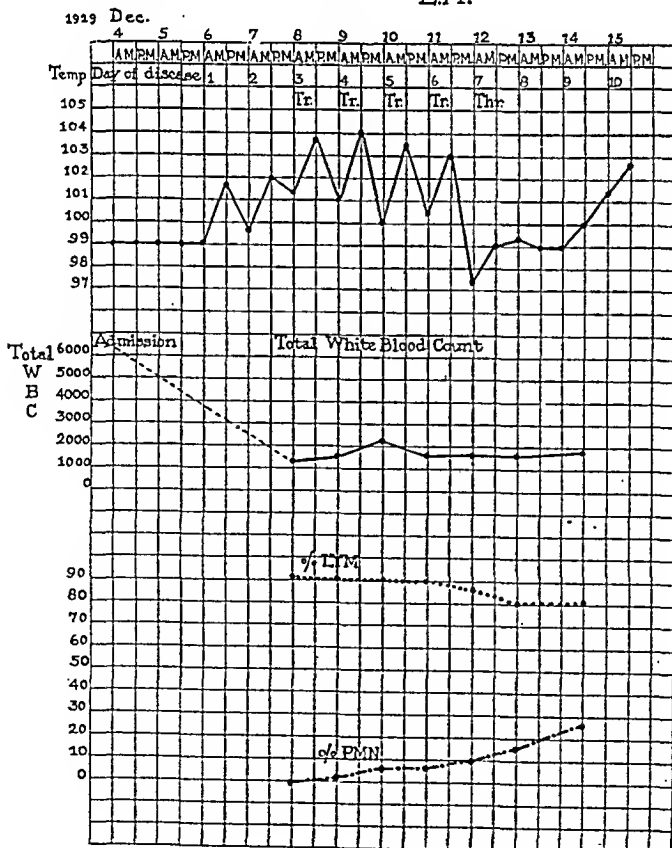


CHART IV.—Tr. transfusion of blood. Thr. appearance of pharyngitis.

CASE VI.—E. A., an elderly woman, aged eighty-two years, who had had a cardiac insufficiency for many years suddenly developed a fever on December 6. The course of the temperature throughout the illness, together with the blood count, is shown on the chart on page 237. With the fever there was moderate prostration, but no localizing symptoms, and physical examination was negative except for the heart. A blood culture was negative. Enlarged lymph nodes were looked for during the course of illness and were not found. On the sixth day of the illness, there was noticed for the first time a diffuse reddening of the throat, and on the pharynx were seen several scattered, small, superficial, white spots resembling *Staphylococcus albus* colonies on a blood plate. On the following day the temperature returned to normal and remained so for forty-eight hours. There then developed symmetrical, pustular, necrotic lesions in the groins. The following day the temperature was higher, there was rapidly progressive edema of one leg with a progressive phlebitis, followed shortly by marked cardiac insufficiency, edema of the lungs and exitus.

It is impossible to say whether or not this terminal episode was in any way related to the immediately previous acute illness from which it was felt she was recovering.

It is also impossible to say how much influence the daily small transfusions may have had on the temperature. This patient was not in the hospital, but her physician saw several of the hospital cases and felt that her acute illness was similar to them in many respects.

CASE VII.—M. K. (Unit No. 85876), a graduate nurse, aged forty years, came into the hospital complaining of general malaise and fever for one week. Since the time of onset of symptoms there was a small white spot on her gum which slowly spread, in spite of treatment with silver nitrate. On the day of admission a new spot appeared and salivation became excessive. On admission she had a temperature of 99.6° , pulse 96, and she appeared flushed and uncomfortable. There were two shallow ulcers in the mouth covered with white slough. There was moderate enlargement of the cervical lymph glands, which were very tender. Her red blood count on admission and throughout her stay of four weeks in the hospital was normal. Her white blood count on admission showed 2800 white blood cells, 73 per cent lymphocytes, 27 per cent monocytes, 0 polymorphonuclears. It was felt that she probably belonged to the agranulocytic angina type of disease. In spite of daily phlebotomies, followed by transfusions, her temperature rose rapidly, reaching 105° on her fifth day in the hospital. Her white blood cells had slowly fallen until they numbered but 1200 on that day, with 2 per cent polymorphonuclears and a very rare myelocyte. An immediately fatal outcome was expected, but on her sixth day in the hospital her temperature began falling and her white count increased, reaching 2900 on the seventh day, with 25 per cent polymorphonuclears, 8 per cent myelocytes, and 1 per cent myeloblasts. Her temperature reached normal on the tenth day in the hospital, the seventeenth day of her illness, and remained normal through the following two and a half weeks. The white count gradually increased, reaching 7000 by the end of her second week in the hospital, with 58 per cent polymorphonuclears; 9000 at the end of her third week, with 66 per cent polymorphonuclears; and was 10,300 at the time of her discharge, with 72 per cent polymorphonuclears. Examination of the mouth lesions revealed a very few Vincent's organisms and a mass of heterogeneous mouth organisms. Blood cultures were repeatedly negative. She has since returned to work and has been without symptoms.

This case and the preceding one represent a more severe type of agranulocytic response, both having no polymorphonuclear leuko-

cytes over a period of several days. These 2 cases probably more closely belong to the accepted syndrome known as agranulocytic angina than do the others.

Bacteriology. Attempts to obtain bacteriologic information have been unsuccessful. The throat lesions have been cultured in every instance and a variety of organisms obtained. A few hemolytic streptococcus colonies were isolated in 2 of the patients, but were not found in the other 4. The whitish, round, very superficial ulcerations observed on the posterior pharyngeal wall were removed as carefully as possible in 3 of the cases and examined by culture and direct smear. The cultures revealed a mass of common mouth and throat organisms without any particular predominate one being found. Direct smears revealed necrotic tissue with scattered various bacteria. These ulcerations were examined for Vincent's organisms in all cases and these were demonstrated in small numbers in three instances. As these organisms are frequently found in any ulcerative condition of the mouth or throat, it was not felt possible to attribute any particular significance to their presence.

Discussion. The syndrome as observed probably represents an unusual reaction on the part of the hematopoietic system to transient throat infection. It is not uncommon to see general systemic reaction preceding, by several days, signs of local inflammation in infections of this sort and this syndrome seems best explained on that basis.

Conclusion. Seven cases are presented of an acute, transient, infectious disease associated with high fever, low pulse rate, enlargement of the lymph nodes, leukopenia, and relative agranulocytosis, the late appearance of queer whitish spots on the posterior pharyngeal wall, and prompt, complete recovery. The etiology is unknown. They represent another variant in the group of infections associated with the agranulocytic type of blood picture.

REFERENCES.

1. Blumer: AM. J. MED. SCI., 1930, 179, 11.
2. Farley: AM. J. MED. SCI., 1930, 179, 214.

PSYCHOGENIC FACTORS IN THE ETIOLOGY OF ULCERATIVE COLITIS AND BLOODY DIARRHEA.

BY CECIL D. MURRAY, PH.D.,

NEW YORK.

(From the Department of Medicine of the College of Physicians and Surgeons of Columbia University and the Presbyterian Hospital, New York.)

IN the course of psychologic investigations in relation to disease—part of the program of the Constitution Clinic—our attention was drawn to a number of cases of ulcerative colitis admitted to the

hospital wards. Preliminary studies directed toward the personality makeup in these patients gave many indications that there were deeper problems to be investigated in the psychophysiologic sphere. Accordingly, thereafter, more emphasis was placed on the patients' life histories and the development of their symptoms. The first four histories obtained are briefly given below, together with an abstract of the physical findings and hospital record. What appears in these cases is a well-marked time relationship between the outbreak of an emotional disturbance and the onset of the symptoms.

For example, in the first case, E. P., an only child, notices the first shreds of mucus in her stools on the very day on which she becomes secretly married. In the second case, C. M., unconsciously conditioned against marriage, finds blood in her stools soon after becoming interested in her first suitor. Later, when engaged to a second one, she develops severe diarrhea with cramps and bloody stools which force her to go to a doctor a few days before the date originally set for her wedding. The case of J. H., is practically the same. In the last case, a boy, aged eighteen years, with a past history showing association of diarrhea with fear, notices blood in his stools from two to five days after a fellow worker threatened to murder him.

The objective side of these histories is all that can be given in a short paper. But the practitioner who has taken the trouble to gain insight into the mechanisms and mannerisms of neurosis will appreciate the subjective feelings which precipitated the pathologic responses in each case.

Case Reports. CASE I.—E. P. ABSTRACT OF MEDICAL RECORD. A married woman, aged twenty-five years, first admission, complaining of diarrhea and vomiting of five days' duration. She had "cholera infantum" in infancy, and three years ago, while abroad, she experienced a bloody diarrhea of two weeks' duration. At other periods of her life she has been constipated, very much so, in fact, since her year abroad, with perhaps only a dozen spontaneous movements in three years. In other respects her health has been excellent. She was married a few months ago, and her last period, due nearly a month ago, was almost completely missed. She has noted no breast changes and does not think she is pregnant, though Dr. X. thinks she may be six weeks along. She was well until a month ago, when she began to note increasing constipation associated with severe, intermittent, abdominal cramps. She went to a hospital, where they gave her a course of colonic therapy; these treatments began to provoke nausea and vomiting, which has grown progressively worse. Four days ago she suddenly began to have diarrhea. Her physician reports: "Stool very foul. Composed of pus, blood and mucus. No amœbæ on one examination. She vomited everything taken by mouth, and the cramps became much more severe. She has not slept much, in spite of morphia. No medications, not even water, have been retained."

Physical examination revealed a well-developed and well-nourished young woman looking quite ill. She was writhing with intermittent abdominal cramps and retching at intervals. There was evidence of moderate dehy-

dration. The abdomen was flat, soft and generally very sensitive to light pressure. No other positive physical findings were noted. Temperature, pulse, and respirations were normal. Her urine contained large amounts of acetone bodies. Blood count normal. Her vomitus gave a faintly positive guaiac reaction. Stools were brown, semifluid, guaiac-negative. No amœbæ seen.

The admission diagnosis was, "acute colitis" (amebic?), acidosis, pregnancy (?).

The diarrhea cleared up almost immediately after admission, but severe cramps and vomiting continued. She was treated with glucose and saline intravenously and subcutaneously and guarded administration of fluids by mouth. Stools were repeatedly negative for amœbæ. The diagnosis of pregnancy was established by gynecologic consultation. A psychologic consultation was requested because the patient managed to give an impression of something obscurely amiss in her marital history and response to treatment.

After a week on the medical wards she was transferred, somewhat improved, to Sloane Hospital for Women.

Total stay in Presbyterian and Sloane Hospitals twelve days.

LIFE SITUATION. The patient is the only child of strict, adoring parents in Georgia. In her final year at college she had a boy friend, but her friendship with him had been marred by the following incident: The young pair had once been stranded at night—too late for her to return to her dormitory. So they had gone to a hotel together to spend the night. Although they had had no sex relations she felt very guilty and apprehensive over the whole affair and wanted to sever all connections with her admirer, but he threatened her, saying: "I will never let another man have you—I will expose you, and no one will believe that we did not have relations that night." From this incident she dates the onset of constipation and her present practice of giving herself a daily enema.

On graduating, she took a position as teacher in an American school in the Near East. She answered the daily letters of her boy friend once a month, still feeling herself in his power, in spite of her effort to get away. Meanwhile the young man had been dismissed from college, had lost one or two jobs, and finally, pining for her love, he had lost his health.

After a year's teaching abroad, she was called home because of her father's illness. She taught school near home for another year, and consented during this period to see her suitor at long intervals. The situation was a great strain upon her, and at the end of the year she came to New York, eager for a stage career, but she needed money first and took a position as cashier in a chain-store.

A cowboy from the West, driver of an armored car, came every evening to collect the money from her cash register, and fell in love at first sight and wrote her, asking for an appointment two weeks ahead. She received him in her rooms. From the first moment he made vain attempts to seduce her but at last he said: "You have stood the crucial test—you must marry me." A month later they were married secretly. On that eventful day she first noticed long shreds of mucus in her stools. Two months after, she heard that her father had died and went South, but she still withheld the news of her marriage from her mother. By the time the young woman got back to New York she found she was pregnant and noticed blood and pus in her stools. Within three days after admission to the hospital she had decided to inform her mother of all that had happened and her colitis had disappeared.

CASE II.—C. M. ABSTRACT OF MEDICAL RECORD. An American secretary, aged thirty years, admitted because of abdominal cramps and diarrhea

of two months' duration. Patient has lived on Long Island most of her life, never in tropics. Always had a hypersensitive nervous system, subject to aches and pains. Four years ago blood streaked stools noticed: blood present intermittently until eight months ago when clots were passed. During this time she was treated for constipation. For two months she has had severe abdominal cramps, urge to defecation with passage only of mucus in many instances, bowels move about 18 times a day. Sent in by her local physician who is said to have found *Amœba histolytica* in rectal mucus. Lost about 22 pounds in eight months.

Physical Examination. Temperature, 99.4; pulse, 80; respirations, 20; blood pressure, 105 systolic, 70 diastolic. Looks chronically ill; tongue is coated; examination otherwise not remarkable, except for slight diffuse tenderness over the entire right abdomen, no spasm.

Laboratory Findings. Hemoglobin, 68 per cent; red blood cells, 4,390,000; white blood cells, 11,000; polymorphonuclears, 55 per cent; leukocytes, 31 per cent; mononuclears, 6 per cent; eosinophils, 8 per cent; urine negative; Wassermann negative. Stool: red blood cells, ++++; white blood cells, ++++. Several questionable nonmotile *Amœbæ histolytica* (?) seen. Proctoscopic examination revealed multiple ulcers of rectal mucosa, typical of amebic colitis, no amœbæ found at proctoscopic examination. Gastric expression: Free hydrochloric acid, 0; total, 16.

Course. After a week's observation put on yatren by mouth and by rectum, receiving 41 gr. in two weeks. Though cramps were relieved somewhat, stools continued about five a day, and continued the same after yatren had been discontinued for a week. She then received stovarsol, 7 gm., in the course of a week, following which her diarrhea and cramps disappeared. However, she developed an arsenic dermatitis, which had practically cleared up at the time of discharge two weeks later, following sodium thiosulphate. A second proctoscopy before stovarsol was started showed some healing, no amœbæ found. During stay here her emotional makeup was found to be unstable, and she was irritable frequently. Due to rapid improvement under stovarsol, it was considered probable that her colitis was amebic in spite of no definite amœbæ having been found here.

Diagnosis on discharge was, chronic colitis; acute poisoning by stovarsol. After discharge from the hospital the patient was married and three weeks later diarrhea returned with blood and she soon had thirty stools a day. She was treated in another city with emetine and stovarsol and gradually improved, having during the exacerbation of her illness lost over 30 pounds. This recurrence of her illness lasted for about four months. For three months she has been perfectly well and has a job here in town. She appears to have a better slant on life and is more composed though even now she avoids intercourse because of a fear that she may have a deformed child. She is careful to avoid raw fruits and coarse foods but except for this she has forgotten her gastrointestinal tract.

LIFE SITUATION. The first conferences with this patient revealed very little except that when she was four years of age her mother died of pneumonia. She was pleasant on all other subjects but touchy about her personal history. "I have supported myself since I was seventeen," she would reply, "and my family affairs have nothing to do with the case." Finally, however, she abandoned her resistance and gave the following history: Three years ago her men friends in the office tried to plan a match for her with another officer in the company. Without having much affection for this person she did, however, go out with him several times, and the thought of marriage as a possibility occurred to her for the first time. Soon after, the duration of her menses diminished to two days and she noticed blood in her stools. She was afraid that the blood was a symptom of cancer, nor would she accept the reassurance of several doctors—none of whom, she thought, took her fear sufficiently seriously.

Two years later she met another man to whom she promptly became engaged during the Christmas season. They planned to get married "in about a year," although there was no tangible reason for such a long engagement. During that year her menses diminished to one day. The year wore on and a few weeks before the following Christmas, she returned from an extended trip. Her sweetheart met her. He had looked up several apartments which he wished to show her, but she could take no interest in choosing between them. She was whole-heartedly in love, but no definite day had been set for the wedding and she was tending to put off the event more and more. Meanwhile, after her return, her colitis became suddenly worse, and a few days before Christmas she went to a doctor for the first time during that year. She was having eight stools a day and was beginning to have cramps, and was admitted to the hospital.

The psychologic background of her case is interesting, not in its novelty, but as a classic. From what has been said, the possibility suggests itself that her fear of cancer derives its exaggerated mental energy from a fear of having a child. When questioned about this she said that the thought of childbirth was, in fact, a mortal fear—she was sure she would die if she had a child. At first she could not account for this. She said she knew practically nothing about sex or childbirth until three years ago. She was asked to think about this problem—how death and childbirth had become so indelibly associated in her mind, but it was not until the following day that she remembered that her mother's death from pneumonia (?) had occurred two weeks after the birth of the patient's youngest sister. She had never thought of that before!

Her aversion to marriage, partly unconscious, also involved a fear of sexual relations, and this fear was likewise definitely conditioned. The patient was the fourth child in a family of six. After the mother's death the father engaged a neighbor to come in as housekeeper, and when the patient was about five years of age, the father married the housekeeper. She was a jealous woman—the children would not kiss her and so she forbade them to kiss the father, whom they adored. When it was pointed out to her that this wound to her early love had come about exclusively through the sex factor—that is, the marriage of the father—she declared: "But that wasn't the worst blow" and then recounted the following story:

When she was about seventeen years of age, her older brother, by that time the only one of the older children still living at home, went away for four years in the navy. She had not been unduly attached to this brother, but during his absence the two had a very voluminous correspondence. In due time the brother returned full of plans to buy an automobile, build a garage, and so on. He was welcomed by his sister as a savior. She and her two younger sisters had borne the brunt of the stepmother's nagging for four years. The first day after his arrival they measured out the site for the garage. But the dreams were not to come true, for within a month the brother was engaged to the stepmother's cousin—a woman ten years older than himself—who "had made a dead set for him, vamped and mothered him."

The patient never spoke to him again. For a while she would lock herself into her room when the brother was home, and he would plead with her through the door. On one occasion he told her that in his four year's service he had not had intercourse. This remark increased her fury—it was the first time she had ever heard the word, but she said she sensed its meaning right away. Soon after this she left home for good. This episode is clearly a repetition in its essential details of the earlier psychic trauma. Again sex had robbed her of what she cared for most.

CASE III.—J. H. ABSTRACT OF MEDICAL RECORD. This is the first admission of a thirty-three-year-old American butcher. Four years ago

he began to have diarrhea and a burning sensation in his rectum. Following this, blood and mucus were passed. He had much tenesmus and passed 3 to 8 stools a day. The condition has persisted almost unchanged since its incipency, except for a few months last summer following certain rectal treatments. He has lost about 40 pounds but most of this has been regained.

P. X.: A well-developed and well-nourished man not appearing ill. Teeth good, tonsils buried. Lungs and heart normal. Abdomen normal. Prostate large and firm. Rectal mucosa: hyperemie, few bleeding areas and shallow ulcerations, some scars.

Laboratory Findings. Red blood cells, 3,740,000; hemoglobin, 88 per cent; white blood cells, 8200; polymorphonuclears, 52 per cent; eosinophils, 7 per cent; Wassermann, negative. Stools: few *Entamoeba histolytica* found, guaiac negative on admission, then ++, then negative. No dysentery bacilli or enterococci. Chest Roentgen ray negative. Urine negative.

Course. He was a proven case of amebic colitis and was therefore given an adequate course of yatren. The drug seems to have been highly successful in this case. On discharge the rectal mucosa was perfectly normal and no amœbæ found. Patient feels in fine shape.

Diagnosis on discharge was, chronic colitis.

The patient, since his treatment with yatren, has had no return of his symptoms for one year, with the exception of some burning in his rectum with attending looseness of stools and constipation for a week following the death of his mother. He has worked continuously since discharge from the hospital.

LIFE SITUATION. The patient is of a very mild, quiet temperament—a salesman in a grocer shop. When he was twenty years of age his father died, and since then he has lived at home with his mother and sister. In fact, he has only been away from his mother for two weeks in his life. When asked if he had ever thought of marriage, he first said he could never leave his mother and sister. But later he said his colitis prevented his getting married. It turned out that four years ago he began keeping company with a girl who lived around the corner. Within a month or two his diarrhea set in, and he stopped work for eight weeks. For two years he averaged about six stools a day—he said his condition was always worse when he resumed the responsibilities in the event of the boss's absence.

Then followed a period free from symptoms. Six months of good health brought him the courage to propose marriage to the girl who had been setting her faith in him for about three years. Her birthday was six weeks off, so he promised to give her a ring on that day. He promptly got the ring, but alas, he got a return of his colitis too. This time he came to the hospital where it was discovered that he had amœbæ in his stools, and where he was cured by specific treatment.

This case shows that the course of the chronic infection is influenced by psychologic factors. Moreover, it is not impossible that the patient's emotional conflict, affecting the gut through disturbed vasomotor, secretory, or peristaltic function, may have lowered the original resistance to the invading organisms.

CASE IV.—I. S. ABSTRACT OF MEDICAL RECORD. A Russian-born Jewish boy, aged eighteen years, first admitted to the hospital June 21, 1928, complaining of bloody diarrhea of five weeks' duration. His past history included typhus, malaria, and scarlet fever in childhood. He came to this country six years ago. His general health had been good up to the time of present illness, but he was of a nervous disposition and, following periods of fear or worry, had noted attacks of abdominal cramps and tenesmus. His occupation was that of a newspaper photographer, strenuous and often exciting work, with irregular hours.

Seven weeks before admission he began to have marked belching after meals; two weeks later he noticed dark-red blood in his stools; stools became loose and more frequent. Dietary treatment by his local physician was ineffective. Two weeks before admission he was having 12 to 13 watery stools a day accompanied by severe abdominal cramps. Stools contained blood and mucus. Weakness and occasional vomiting during preceding three days.

Physical examination showed a thin pale Jewish boy, mildly acutely ill, but in no apparent discomfort. Tongue clean, heart rate somewhat rapid, abdomen soft, not distended, with moderate generalized tenderness on deep pressure. Pulse, 96; temperature, 99.6°; blood pressure, 110 systolic, 50 diastolic; weight, 115 pounds. Blood count: hemoglobin, 55 per cent; red blood cells, 3,150,000; white blood cell, 7500; polymorphonuclears, 64 per cent; lymphocytes, 27 per cent; eosinophils, 9 per cent. Slight pallor of red cells. Blood Wassermann, negative. Blood Widal, negative. Stool: fluid, dark red bloody material. Microscopic examination: loaded with red blood cells and pus cells. Guaiac + + + +. Stools negative for amoebæ, *Bacillus dysenteriae* and *Bacillus typhosus*.

Course. Patient ran an irregular fever, up to 103°, and continued to have frequent bloody stools, abdominal cramps and anorexia. Apprehensive and depressed. Several transfusions seemed to help his condition somewhat. Mental attitude and general condition improved after psychotherapy was started. Discharged improved, though he still had some bloody diarrhea, on July 21, 1928.

Readmitted nine days later with the symptoms of pain in left flank, blood-streaked stools and nausea. Examination showed increased tenderness over whole colon. Weight, 110 pounds; hemoglobin, 38 per cent; red blood cells, 2,050,000; proctoscopy showed several large superficial ulcers covered with mucopurulent exudate.

Course. Temperature normal, except for a reaction following transfusion. Spleen became palpable. Given belladonna and a course of yatren, also Blaud pills. He improved and gained in weight. Stools 4 to 6 daily, but without blood. Discharged and went to the country August 28, 1928.

Through the autumn patient did fairly well, gained weight up to 140 pounds, continued to have frequent stools with blood and pus.

Third admission December 31, 1928, for special study, culture of stools, etc. Proctoscopy showed edema of mucosa, and multiple miliary abscesses. Cultures of stools were taken. Discharged January 11, readmitted January 21, 1929, and vaccine and filtrate injections (prepared according to Barger's technique) were given. General course unchanged. Discharged February 5, 1929.

Vaccine injections were continued three times a week. Patient's abdominal condition was about the same but his anemia increased. Readmitted March 8. Following transfusion, blood count improved to hemoglobin, 56 per cent; red blood cells, 4,300,000. Again his diarrhea improved, but anemia and weakness increased during the next two months. Hemoglobin, 28 per cent; red blood cells, 2,800,000.

Readmitted for the sixth time June 7, 1929. Pale and chronically ill. Abdomen soft, with marked tenderness in left lower quadrant. Temperature, 103°; pulse, 120.

Course. Tenderness over whole colon became acute and remained so. Stools contained only traces of blood. Patient continued to run an irregular fever, developed a profound toxemia and prostration, was unable to take nourishment and wasted rapidly. He developed a marked glossitis, and a curious and unexplained subcutaneous edema of the cervical and anterior thoracic regions. Transfusions and other measures were ineffective. As a

last resort, ileostomy was performed on July 15; after this he seemed to improve slightly, but weakened again and died July 21, 1929.

Final Diagnosis: Chronic colitis, secondary anemia.

LIFE SITUATION. In the first interview the patient said he had worked in a machine shop in a basement for two years without a vacation. He went to high school evenings. Sundays he did special work near his home. He is the sole support of his mother and sisters, with whom he emigrated from Russia six years ago. The patient remembers it was on December 15 he noticed blood in his stools for the first time. Five months later he began having severe cramps and diarrhea and entered the hospital.

Referring to his childhood, the patient described the cramps which he had felt at the times, when, in Russia, the Red Army had looted his home. Eventually he and his family were thrown out of the home, and shortly after this he contracted typhus. In the process of talking about these episodes, the patient had what he said was the most severe cramp he had ever experienced. He remembered also having diarrhea in infancy and how, at the time, his nurse used to blacken her face to frighten him into eating the raw eggs which were prescribed. He denied any other frights or fears.

In the second interview, however, he told of how his boss had hired a helper for him in the fall. The helper was a moron or half insane, the fifty-year-old brother of the boss. The patient had to instruct him in the routine of the work, but he made many mistakes for which the patient, who did not dare complain, was blamed by the boss. One day, about December 10, (that is, about five days before the first appearance of blood in the stools) the helper, during a quarrel, threatened to kill him. When he felt especially nervous alone in the basement with this madman. Finally the boss saw for himself that he would take refuge in the toilet. Finally the boss fired him. But the patient's fear was no asset to his business and therefore told him that the brother had said he was coming down some day to knife him.

The patient had always quarreled with his boss, who was very cranky, and now things were becoming intolerable. But his family being entirely dependent upon his weekly earnings, he had to put up with it all until his colitis settled the question for him.

Discussion. It is well known that a state of emotion is often accompanied by hypermotility or spasticity of the colon and probably also by hypersecretion and vasomotor disturbances.^{1, 2, 3} The exact mechanism of this phenomenon is unknown, but the reality of an actual nervous link between mental states and colon disturbances is virtually proved by the abundance of histories which reveal a close time relationship between the mental and physical symptoms. The cases reported above show this relationship in a very striking manner, but more than that, they show how serious the physical condition can become in one or more of the following circumstances, namely: (1) if the emotional conflict is deep-seated, or chronic or not easily settled; (2) if there is a specific organism, and, vague though it is, we must add, (3) if the individual is predisposed in some way by heredity early training, general physical or nervous makeup, etc., to colon afflictions.

In connection with this third factor there were some noteworthy personality characteristics which were common to 12 patients which I observed. Draper and McGraw^{4, 5} have emphasized the

fear component in cases of gastric ulcer and this observation especially would apply to cases of bloody diarrhea and ulcerative colitis. They describe the gastric-ulcer type as one showing "little stability of mood, rapid expenditure of emotional energy, quick adjustment to changes in the environment and great fearfulness. The ulcer patients are ideal opportunists and mental sprinters; and while they have little endurance, they are promptly rehabilitated by food, short periods of rest and the relief of anxiety."

The outstanding trait in colitis patients, besides fearfulness, is their emotional immaturity, and in this respect they differ from the gastric-ulcer individuals who give the impression of a greater emotional development. It goes without saying that diarrhea is an infantile response to fear. The organization of the infant is presumably such that fear is often expressed by excitation of the colon, and thus a pattern may be laid down and not outgrown.

Aside from their physical symptoms, the colitis patients revealed definite childish elements in their makeup. Of 7 men who were interviewed, all were tied to their mothers except one who had found a mother substitute in an older sister. Several of these men had never been away from their mothers for more than thirty days in their whole lives. None of these men were married, and for the most part the onset of their colitis was associated with the conflict between the mother-tie and desire for marriage—psychologically a repetition of the birth experience. Of the 7 men, the presence of ulcers was proved in 5 cases, and the persistent appearance of bloody stools in all. Our language sums up the story of these patients in the phrases "They feel cramped" and "They haven't got the guts."

Of 5 women with bloody stools, in 2 of whom the presence of ulcers was proved in the hospital, 3 were married as follows: One to a man her own age who had been virtually living in the home of his wife's parents; the second was married to a man twice her age—an inadequate father substitute—from whom she tried to free herself, but got colitis in the attempt; the third, E. P., was secretly married. Of the remaining 2 women, one, C. M., was engaged, but her colitis and her unconscious mental attitude were interfering with marriage. The other was unapproachable on the subject of marriage so I could infer very little as to her conscious attitude about this matter, or in fact any other matter.

Although nothing can be absolutely proved as yet from these cases, the evidence is very suggestive that the more severe cases of colitis with bloody diarrhea and ulcerations have a psychologic factor in their etiology of the kind similar to that which has long been recognized as existing in some simple diarrheas and in mucous colitis.

Prolonged psychoanalysis is usually economically out of the question for ward patients who cannot afford the time for it. But

we have nevertheless been encouraged to put greater effort into work along psychotherapeutic lines not only while the patients are undergoing intensive medical treatment in the wards, but also after their discharge from the hospital by interviews in the out-patient clinic.

Conclusions. Investigation into the life histories and mental attitudes of a series of 12 patients suffering from bloody diarrheas or ulcerative colitis revealed a close association in time between the emergence of a difficult psychologic situation and the onset of the symptoms.

Mental conflicts concerned with marriage were more commonly found than other types of situations which might evoke anxiety. In each case the patients faced their problems in an inadequate, infantile manner.

If the pathologic process has not progressed too far, a thorough investigation into the patient's life and mental attitude is indicated and may afford opportunity for much-needed psychotherapy.

REFERENCES.

1. Mallory, W. J.: Medical Aspects of Colitis, *J. Am. Med. Assn.*, 1928, 90, 601.
2. Riesman, D.: History Taking and Physical Examinations in Digestive Disorders, *J. Am. Med. Assn.*, 1928, 90, 1992.
3. Henry, G. W.: Emotions and Digestive Functions, *J. Am. Med. Assn.*, 1927, 3, 19.
4. Draper, G., and McGraw, R. B.: Studies in Human Constitution: The Psychological Panel, *AM. J. MED. SCI.*, 1927, 174, 299.
5. Draper, G.: *Disease and the Man*, Kegan Paul, London, 1930.

A NEW INTERPRETATION OF THE VAN DEN BERGH REACTION.

BY HIRAM F. SNIDER,

AND

JOHN G. REINHOLD,

PHILADELPHIA.

(From the Biochemical Laboratories of the Philadelphia General Hospital and the Graduate School of Medicine of the University of Pennsylvania, Philadelphia.)

MANY attempts have been made to explain the differences in reactivity of sera from jaundiced individuals with a sulfanilic-nitrous acid diazo reagent when this reagent is added directly to the serum. Van den Bergh¹ and McNee² believed that two types of pigment were involved, a rapidly reacting type in obstructive jaundice and a slowly reacting type in hemolytic jaundice. On this basis the reaction was advocated as a method for the differential diagnosis of jaundice. Other explanations for the prompt and delayed type of

reactions have been based on differences in solution state of the pigment, the extent of its combination with base, adsorption on serum proteins, and the effect of bile salt accumulation in the serum in obstructive jaundice. It was shown by Thannhauser and Andersen³ and Davies and Dodds⁴ that state of oxidation and by the latter also, that hydrogen ion concentration were important factors in determining the velocity of reaction. However, none of the explanations previously given are adequate and most of them have been discarded.

For the estimation of bilirubinemia in this laboratory the icterus index has been determined in conjunction with van den Bergh's direct procedure. A close relationship, dependent on the concentration of bile pigment, was observed between the two tests. Immediate reactions practically always occurred in sera having high icterus indices, while delayed reaction sera invariably had low indices. Biphasic reactions were associated with intermediate icteric index values. The possible effect of concentration was recognized by van den Bergh¹ who cites experiments in which sera from individuals having obstructive jaundice were diluted to a light yellow color, but continued to give an immediate reaction. Hence he concluded that the differences in reactivity were not dependent upon differences in the amount of bile pigment present. The degree of dilution in his experiments is not stated, but it could not have been great or the reduced buffering capacity of the serum would have checked the reaction. Only a few experiments were made by van den Bergh and no other investigation of this phase of the diazo test for bilirubin has been found. There is abundant evidence from other sources that concentration is of the greatest importance. Mann, Sheard, and Bollman⁵ in their studies of blood bilirubin noticed that the serum gave first a delayed and later a biphasic reaction following the removal of the abdominal viscera. During the same interval the bilirubin content of the serum was increasing rapidly. Barron and Bumstead⁶ and Mayo and Greene⁷ after obstructing the common ducts and excluding or removing the gall bladder obtained first delayed or biphasic and then immediate* reactions as the jaundice increased. The clinical observations of Friedmann and Strauss⁸ and Mogen⁹, who found that the van den Bergh reaction changes with the severity of jaundice, give additional support to the concentration hypothesis.

An experimental study of bilirubin solutions by means of the van den Bergh test has confirmed the importance of the concentration of bilirubin and has shown that it is the principal factor which determines whether immediate, biphasic, or delayed reactions will occur.

Methods. Icterus index determinations were done by the technique described by Murphy.¹⁰ Phosphate buffer solution (pH 7.4)

* "Direct" is used in both papers in the same sense as prompt or immediate.

was used in place of 0.9 per cent sodium chlorid for diluting the serum. When the icterus index was greater than 25 the serum was diluted until it matched the standards between 10 and 15. Kerppola and Leikola¹¹ have pointed out that bilirubin behaves as an indicator, consequently the color intensity of a bilirubin solution does not indicate the true quantity of pigment unless the pH is controlled.

For the direct or qualitative van den Bergh test the procedure of Lepchine, described by McNee and Keifer,¹² was used. A sheet of paper used as a background was helpful in following the development of color in the tubes. The time required for the color to appear and the time at which it reached its maximum intensity was measured with a stopwatch. The tests were done not longer than eight hours after taking the specimen. Temperature of the reacting materials was controlled in the experimental work, but was neglected in all except the more recent determinations included in Table I. The effect of temperature on the rate of reaction will be discussed later.

The reactions were classified as *immediate* when the color appeared promptly and reached a maximum within sixty seconds; *biphasic* when the color appeared promptly but required more than a minute to reach maximum intensity; and *delayed* when the initial color appeared later than one minute but before five minutes. Reactions starting after five minutes were called negative. Extending the observation period beyond this time introduces possibilities for error due to side reactions. It was often difficult to decide whether a given reaction was immediate or biphasic, hence the term *immediate-biphasic* was used in the tables to describe those instances in which the distinction could not be made.

Relationship Between the Qualitative van den Bergh Reaction and the Icterus Index. In Table I the results of 721 parallel determinations of the van den Bergh reaction and the icterus index are classified according to the type of reaction occurring within selected limits. These tests represent clinical determinations of this laboratory made over a period of five years by six workers. They were done for the most part without special precautions to control color development, temperature, or age of the specimen. Although there is some overlapping in the table the relationship between concentration of pigment and the type of van den Bergh is clearly defined. The overlapping is explained by the many possibilities for experimental error and by the well known difficulty of determining the type of some reactions.

Dilution Experiments with Bilirubin Dissolved in Serum. In these experiments the bilirubin* was dissolved in a slight excess of $\frac{N}{10}$ sodium hydroxid, after which the excess alkali was neutralized with

* Three samples of bilirubin were used. Two were obtained from the Eastman Kodak Company and one from the Theodor Schuchardt Chemische Fabrik.

$\frac{N}{20}$ hydrochloric acid. The slight change in color from an orange to a yellow and the simultaneous formation of a precipitate was used as an endpoint. The precipitate was then redissolved by adding 1 drop of $\frac{N}{10}$ sodium hydroxid. The resulting solutions were faintly alkaline to litmus and acid to phenolphthalein. They were made as quickly as possible so as to avoid the auto-oxidation which takes place in alkaline solution. This concentrated solution was added to clear unhemolyzed human serum. Various dilutions were prepared from the resulting mixture by adding portions of it to serum. In this way a graduated series of serum solutions of bilirubin was obtained. These were treated with the diazo solution as described above, except that it was necessary to increase the reactivity by the addition of alkali in order to obtain reactions having rates comparable to those in jaundiced serum.

TABLE I.—THE RELATIONSHIP BETWEEN THE ICTERUS INDEX AND DIRECT VAN DEN BERGH REACTION.

Icterus index.	Total number.	Van den Bergh.							
		Negative.		Delayed.		Biphasic.		Immediate.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
1- 3	20	19	95	1	5				
4- 6	174	149	85	25	15				
7- 9	89	35	39	51	57	3	4		
10- 12	67	4	7	53	79	10	14		
13- 15	26	15	57	11	43		
16- 18	13	1	8	3	23	9	69		
19- 25	45	1	2	3	7	40	89	1	2
26- 35	41	6	15	32	78	3	7
36- 45	37	2	5	25	68	10	27
46- 55	22	1	5	13	59	8	36
56- 65	27	13	48	14	52
66- 75	23	1	5	4	13	18	82
76- 85	12	1	8	11	92
86- 95	25	3	12	22	88
96-105	18	2	11	16	89
106-115	16	2	12	14	88
116-124	15	15	100
125-135	6	6	100
136-145	15	1	7	14	93
146-155	6	6	100
156-165	—								
165-175	4	4	100
176-185	5	5	100
186-195	5	1	20	4	80
196-285	10	10	100

Solutions of bilirubin in serum reacted much more slowly than did jaundiced sera having the same color index. The addition of small amounts of disodium phosphate, sodium acetate, or sodium hydroxid accelerated the reaction. In the experiments reported,

disodium phosphate was used to increase the rate of reaction so that it was approximately that observed in jaundiced serum. For this purpose 1 drop of a 10 per cent solution was added to each tube. Since the concentration of sodium phosphate was the same in all tubes the results would not be influenced for the purpose of comparison by this factor. The concentration of sodium hydroxid used in preparing the bilirubin solutions which would have varied with the amount of bilirubin added was likewise made the same in all tubes. The accelerating effect of alkali noticed in these instances has been reported by others (Davies and Dodds;⁴ Newman;¹³ and Maeda and Morishima¹⁴) and appears to be related in part to the increased solubility of the added bilirubin, since bilirubin is relatively insoluble at acid reactions, but it is easily soluble in alkaline solutions. The solutions of bilirubin in serum were acid after the addition of the diazo reagent.

Representative data obtained by diazotizing serum solutions containing varying amounts of bilirubin are presented in Table II. The tubes giving immediate and delayed reactions differed only in the quantities of bilirubin each contained. These reactions closely resembled those observed in serum from cases of jaundice.

TABLE II.—EXPERIMENTS WITH BILIRUBIN DISSOLVED IN HUMAN SERUM.

	Icterus index.	Initial color.		Maximum color.		Van den Bergh.
		Min.	Sec.	Min.	Sec.	
Exp. 1	140	0	0	0	40	Immediate.
	75	0	2	0	55	Immediate.
	40	0	5	1	55	Biphasic.
	20	1	5	3	40	Delayed.
	10	1	50	4	30	Delayed.
	3	8-10	...	Negative.
Exp. 2	140	0	0	0	35	Immediate.
	110	<1	...	1	25	Immediate-biphasic.
	60	<1	...	3	...	Biphasic.
	40	<1	...	4	10	Biphasic.
	18	>1	...	5	20	Delayed.
	12	>5	...	7	...	Negative.
	4	>5	...	10	...	Negative.
	110	0	0	1	30	Immediate-biphasic.
Exp. 3	60	0	20-30	3	5	Biphasic.
	40	0	35-40	4	10	Biphasic.
	18	>1	...	5	20	Delayed.
	12	>1	...	5	30	Delayed.
	6*	3	50	Delayed.

* Diluting serum gave a delayed reaction.

Dilution Experiments Using Jaundiced Serum. Additional evidence was obtained by diluting serum from severely jaundiced patients with varying quantities of normal human serum. The van den Bergh

reaction and the icterus index were then determined. Typical results are given in Table III. Immediate, biphasic, delayed, and negative reactions occurred in the various dilutions of the same specimen, depending again on the concentration of bilirubin. The results were less clear when dog serum was used because of the increased speed of reaction in this medium. If the dog serum remained in contact with the cells overnight, similar dilutions (freshly prepared) reacted less rapidly. A similar but less noticeable effect of standing was observed when human serum remained in contact with cells for six hours or more. Under these conditions there are changes in the serum which have an inhibiting effect on the van den Bergh reaction. When phosphate buffers were used as diluents all of the reactions continued to be immediate regardless of the dilution.

TABLE III.—DILUTION EXPERIMENTS WITH JAUNDICED SERUM.

Date.	Patient.	Diagnosis.	Dilu- tion.	Icterus index.	Initial color.		Maximum color.		Van den Bergh.
					Min.	Sec.	Min.	Sec.	
April 8	J. S.	Gall-bladder disease	0 1:1 1:5 1:20	45 20 8 Precipitated 1 by diazo reagent 20	Immediate. Biphasic. Delayed.
Aug. 9	H. S.	...	0 1:2 1:6 1:30	120 60 22 4	Immediate. Immediate. Biphasic. Delayed.
Dec. 30	G. B.	Common duct obstruction	0 3:1 1:4 1:8 1:40	160 120 35 20 4	0 0 0 1 5	2 2 50 15 30	1 2 4 5 8	25 10 ..	Immediate- biphasic. Immediate- biphasic. Biphasic. Delayed. Negative.
May 28	A. M.	Catarrhal jaundice	0 1:20 1:40	185 9 4	.. 0 3	.. 20 2 0 ..	Immediate. Biphasic. Delayed.
July 10	C. B.	Adenoma of liver, cirrho- sis	0 1:50 1:333 1:1000	210	0 0 3 5	1 15-20	0 2 8-10 ..	30	Immediate. Biphasic. Delayed. Negative.
July 25	L. L.	Cholangitis; myelogenous leukemia	0 1:7 1:90	285 40 3	.. 0 2	.. 20 40	.. 2 3 50	Immediate. Biphasic. Delayed.

The Effect of Alcohol. The effect of alcohol like that of alkali is to cause a marked increase in the velocity of diazotization of bilirubin in serum. Its action in phosphate buffer solution is similar. This disproves the older explanation of the rôle of alcohol which stated that the increased rate of reaction was due to the liberation

of bilirubin by the alcohol from a hypothetical bilirubin-protein complex. The latter supposedly was characteristic of hemolytic jaundice.

Effect of Temperature. A greater incidence of immediate reactions when the temperature of the laboratory was unusually high suggested an investigation of the effect of temperature on the velocity of diazotization of bilirubin. The marked influence of this factor on the rate of color appearance is shown by experiments made with jaundiced serum. The results are presented in Table IV. The experiments with jaundiced serum and bilirubin dissolved in normal serum were carried out at 20° C.

TABLE IV.—EFFECT OF TEMPERATURE.

1.	Icterus index, 210 Van den Bergh	Temperature, 28° C. Immediate (maximum color, 30 to 40 sec.)	Temperature, 10° C. Biphasic (maximum color, 2 min. 50 sec.)
2.	Icterus index, 17 Van den Bergh	Temperature, 30° C. Biphasic (initial color, 25 sec.)	Temperature, 15° C. Delayed (initial color, 3 min.)

Discussion. The correlation between type of van den Bergh and origin of jaundice has been widely accepted and used as a method for differential diagnosis. Actually the relationship is only incidental to the group differences in concentration of serum bilirubin between jaundice of the hemolytic and obstructive types. In the former there are comparatively moderate changes in serum bilirubin, in the latter much larger increases are common. An examination of a number of cases indicates that hemolytic jaundice when accompanied by marked bilirubinemia gives biphasic rather than delayed reactions. Although immediate reactions have not been observed in this group, neither has there been an instance in which the concentration of serum bilirubin was sufficient to make an immediate reaction probable. On the other hand, delayed reactions frequently occur in mild obstructive jaundice. The type of reaction throughout has been independent of the source of the pigment.

In general, the relationship between icterus index and direct van den Bergh reaction is confirmed in the literature. However, if the indirect van den Bergh reaction is used to determine bilirubin, the velocity-concentration relationship does not hold as well, judging by the results of van den Bergh¹ and Ravdin.¹⁵ The lack of agreement is most conspicuous at higher pigment concentrations where the experimental errors are large.

The effect of changing the medium in which the bilirubin was

dissolved was mentioned in the description of the experimental work. The decrease in the velocity of reaction caused by leaving the diluting serum in contact with the cells probably can be explained by the lowered pH and buffer capacity of the serum treated in this way. The sensitiveness of the reaction to acidity has already been mentioned. Obviously the results of the dilution experiments might be explained by the increasing concentration of an inhibitory substance, and McNee and Keefer¹² state that globulin has an inhibiting action. However, in several experiments freshly prepared serum protein added to jaundiced serum had no effect on the diazo reaction. Furthermore, the correlation of serum color and velocity of diazotization shown in Table I is opposed to such an explanation.

Although there is no valid theoretical basis for the use of the van den Bergh reaction for identifying the various types of jaundice, it remains a useful qualitative test for bilirubin. A clinical survey has substantiated the explanation given by the experimental work.

Summary. The type of direct van den Bergh reaction observed in serum depends upon the concentration of bilirubin.

In the cases here reported an immediate van den Bergh reaction was associated with a high icterus index and a delayed van den Bergh with a low icterus index.

The van den Bergh reaction changed from negative to delayed, then to biphasic, and finally to immediate as increasing amounts of bilirubin were added to human serum.

Dilution of a jaundiced serum with normal serum changed the van den Bergh reaction of the former from immediate to delayed.

The temperature of the reacting materials was shown to be an important factor.

NOTE.—The writers are indebted to Drs. I. S. and E. G. Ravdin for their criticism of the manuscript.

REFERENCES.

1. Hijmans Van den Bergh, A. A.: *Der Gallenfarbstoff im Blute*, Leiden, 1918.
2. McNee, J. W.: *Quart. J. Med.*, 1922-1923, **16**, 390.
3. Thannhauser, J. S., and Andersen, E.: *Deutsch. Arch. f. klin. Med.*, 1921, **137**, 179.
4. Davies, D. T., and Dodds, E. C.: *Brit. J. Exper. Path.*, 1927, **8**, 316.
5. Mann, F. C., Sheard, C., and Bollman, J. L.: *Am. J. Physiol.*, 1928, **74**, 49.
6. Barron, E. S. G., and Bumstead, J. H.: *J. Exper. Med.*, 1928, **47**, 999.
7. Mayo, C., and Greene, C. H.: *Am. J. Physiol.*, 1929, **89**, 280.
8. Friedmann, J. C., and Strauss, D. C.: *J. Am. Med. Assn.*, 1924, **82**, 16.
9. Mogen, H. G.: *Lancet*, 1929, **216**, 1187.
10. Murphy, W. P.: *Arch. Int. Med.*, 1926, **37**, 797.
11. Kerppola, W., and Leikola, E.: *Skand. Arch. Physiol.*, 1928, **54**, 120.
12. McNee, J. W., and Keefer, C. S.: *Brit. Med. J.*, 1925, **ii**, 52.
13. Newman, C. E.: *Brit. J. Exper. Path.*, 1928, **9**, 112.
14. Maeda, T., and Morishima, T.: *Japan J. Gastroenterol.*, 1929, **1**, 155; *Abstract, Chem. Abstracts*, **24**, 386.
15. Ravdin, E. G.: *AM. J. MED. SCI.*, 1925, **169**, 850.

PRELIMINARY NOTES ON BACTERIOLOGIC STUDIES AND TREATMENT OF CHRONIC EPIDEMIC ENCEPHALITIS.

By WINIFRED BAYARD STEWART, A.M., M.D.,

ASSISTANT NEUROLOGIST AT THE PHILADELPHIA GENERAL HOSPITAL; ASSOCIATE IN
NEUROLOGY AT THE WOMAN'S MEDICAL COLLEGE OF PHILADELPHIA;
INSTRUCTOR IN NEUROLOGY AT THE MEDICAL SCHOOL
OF THE UNIVERSITY OF PENNSYLVANIA,

AND

MARY JARDINE EVANS, PH.D.,

ASSISTANT BACTERIOLOGIST AT THE PHILADELPHIA GENERAL HOSPITAL,
PHILADELPHIA, PA.

ALTHOUGH the etiology of epidemic encephalitis has been the subject of much research during the past ten years, thus far no serious attempt has been made to discover whether there is any relationship between this disease and the Pfeiffer bacillus. It was to determine this relationship that the following work was begun at the Philadelphia General Hospital. For our studies we have chosen cases of chronic epidemic encephalitis; the wealth of clinical material of this type as well as the absence of the fever complicating acute encephalitis—a factor likely to bring out latent agglutinations—determined our choice.

Thus far 165 cases have been studied. Of these 151 present the Parkinsonian syndrome, 7 behavior changes, 5 early Parkinson's with complicating psychoses, one encephalomyelitis and one amyotrophic lateral sclerosis. All available cases of Parkinson's syndrome were studied. No attempt was made to differentiate the encephalitic from the idiopathic or arteriosclerotic types clinically. All were taken regardless of age, previous history of encephalitis, or the presence of advanced arteriosclerosis.

Of these 165 cases, we have complete data on 162. Eighty-four patients gave a history of acute encephalitis, 71 a history of influenza, 60 of these having had this infection in 1918. Twenty-nine gave a history of both acute encephalitis and of influenza and 36 of neither. Two children, one with Parkinson's syndrome and behavior changes, the other with behavior changes alone, gave a history of neither influenza nor of acute encephalitis but their respective mothers had influenza when they were born.

The yearly curve of incidence of acute encephalitis for our cases follows the curve reported by the Matheson Commission¹ except for the fact that our peaks occur in 1920 and 1923 instead of in 1920 and 1924, as they report. For the cases studied, the duration of symptoms of chronic encephalitis was from six months to twelve years. The development of manifestations of chronic disease occurred up to ten years after acute encephalitis and after influenza, if we may assume that this is an antecedent, up to twelve years.

Our control series comprises 122 cases. An attempt was made to have a fair distribution of cases both as to disease and to environment. Thirty-nine were outpatients, the remainder ward patients. Of the latter approximately one-half were patients on an active medical ward, the other half on the rather stationary neurologic ward under the same environmental conditions as the patients suffering from chronic encephalitis.

A history of influenza was elicited from 20 per cent of these control patients. One case had acute epidemic encephalitis in 1921 with apparent complete recovery. Of the neurologic cases 5 were diagnosed multiple sclerosis, 5 Huntington's chorea, 3 Sydenham's chorea, 2 spasmodic torticollis, 2 lenticular degeneration and 5 syphilis, 2 of which had been treated. The remainder consisted of the usual run of cases in wards and clinics.

Bacteriologic Studies. *A. Cultures.* Nasopharyngeal cultures were obtained from 114 cases of chronic epidemic encephalitis and from 37 controls. Two plates were streaked for each case, one of brown-blood agar and one of red-blood agar. The colonies of Pfeiffer bacillus could be studied with ease on the brown-blood plates, while colonies of the other organisms appeared distinctly on the red-blood agar plates. The Pfeiffer bacillus was present in 100 per cent of the nasopharyngeal cultures of patients suffering from chronic epidemic encephalitis and in 46 per cent of the control cases. This latter percentage held for both in- and outpatients. Other organisms found were *Streptococcus viridans* 63 per cent, *Pneumococcus* 43 per cent, *Micrococcus catarrhalis* 38 per cent, *Streptococcus hemolyticus* 35 per cent, *Anhemolytic streptococcus* 16 per cent, *Staphylococcus* 10 per cent, *Friedländer's bacillus* 5 per cent, *Diphtheroids* 5 per cent. These organisms showed approximately the same frequency in the cultures both from the experimental series and from the controls.

B. Serologic Studies. The agglutination technique followed was according to the method of Evans and Small.² A loop of culture of Pfeiffer bacillus was streaked on brown-blood agar plates. The resulting growth was washed off in broth, centrifugalized, resuspended in infusion broth and heated to 85° C. for one hour. The suspension was then standardized to one billion organisms per cubic centimeter. The patient's serum was diluted from 1 to 10 up to 1 to 1280, equal amounts of the suspension was added to these tubes of diluted serum and the tests were incubated in a water bath at 50° C. for eighteen hours. Naked-eye readings were made.

For the flocculation tests, eighteen-hour brown-blood broth cultures were filtered through a Berkefeld filter and the filtrate tested for sterility. Equal amounts of culture filtrate were added to the patient's serum, diluted as for the agglutination tests, and naked-eye readings were made after the tests had stood at room temperature for eighteen hours.

STEWART AND EVANS:

TABLE I.—AGGLUTINATION AND FLOCCULATION REACTIONS IN CHRONIC EPIDEMIC ENCEPHALITIS. (PFEIFFER BACILLUS WAS FOUND IN NASOPHARYNGEAL CULTURES OF ALL CASES.)
(Hospital of the University of Pennsylvania)

Name.	Age.	Sex.	Flu.	A. E.	C. E.	Park.	Agg.	Floc.	For. agg.	
P. F.	44	M.	0	0	1927	2	1:20	1:40	B. Mel.	Neg.
H. W.	21	M.	1918	1925	1928	1	1:80	1:80	B. Mel.	Neg.
N. K.	27	F.	0	1920	1920	4	1:20	1:40	S. Vir.	Neg.
D. B.	30	M.	1918	1923	1927	2	1:40	1:40	S. Vir.	Neg.
A. W.	24	M.	0	1924	1924	2	1:160	1:40	S. Vir.	Neg.
E. D.	58	F.	0	0	1927	1	1:80	1:20	S. Vir.	Neg.
W. S.	28	M.	1918	0	1926	2	1:80	1:40	S. Vir.	Neg.
G. S.	46	M.	0	0	1929	1	1:80	1:40	S. Vir.	Neg.
A. K.	53	M.	1920	0	1927	2	1:80	1:40	S. Vir.	Neg.
J. S.	14	M.	0	1926	1926	1	1:80	1:160	S. C. A.	Neg.
J. L.	30	M.	0	1920	1920	1	1:40	1:80	S. C. A.	Neg.
L. B.	40	F.	0	0	1926	1	1:40	1:40	S. C. A.	Neg.
W. H.	36	M.	0	1918	1918	1	1:80	1:80	S. C. A.	Neg.
R. S.	42	F.	1921	0	1926	1	1:40	1:20	S. C. A.	Neg.
J. M.	23	M.	0	1928	1928	2	1:80	1:40	S. C. A.	Neg.
P. M.	60	M.	0	0	1929	4	1:40	1:40	S. C. A.	Neg.
C. P.	40	M.	0	1920	1928	1	1:80	1:40	S. C. A.	Neg.
M. H.	37	M.	1918	1920	1928	1	1:320	1:80	S. C. A.	Neg.
E. S.	25	F.	1918	1925	1925	2	1:80	1:40	S. C. A.	Neg.
S. P.	39	M.	1924	0	1926	1	1:40	1:40	S. C. A.	Neg.
V. K.	16	M.	0	1920	1928	4	1:40	1:80	S. C. A.	Neg.
S. G.	47	M.	0	0	1926	1	1:40	1:80	S. C. A.	Neg.
J. S.	40	M.	0	0	1928	1	1:16	1:80	S. C. A.	Neg.
M. R.	22	F.	1918	0	1928	2	1:80	1:40	S. Vir.	Neg.
J. G.	40	M.	0	0	1928	1	1:160	1:160	S. C. A.	Neg.
H. C.	26	M.	0	1924	1924	1	1:80	1:40	S. C. A.	Neg.
M. C.	38	M.	1918	0	1922	1	1:80	1:40	S. C. A.	Neg.
G. F.	40	M.	0	1928	1929	1	1:20	1:40	S. C. A.	Neg.
M. Y.	29	F.	1918	0	1928	1	1:160	1:160	S. C. A.	Neg.
					1929	E.M.	1:80	1:40	S. C. A.	Neg.
							1:20	1:40	S. C. A.	Neg.

(Women's College Hospital)

M. P.	58	F.	0	0	1929	1	1:20	1:20	S. C. A.	Neg.
W. C.	28	F.	1918	0	1929	1	1:40	1:40	S. C. A.	Neg.
H. W.	42	M.	1918	0	1926	2	1:40	1:40	S. C. A.	Neg.

(Episcopal Hospital)

J. K.	46	M.	1918	0	1926	2	1:80	1:80	S. C. A.	Neg.
J. B.	44	M.	0	1925	1925	3	1:20	1:40	S. C. A.	Neg.
M. M.	18	F.	1918	1919	1919	2	1:160	1:160	S. C. A.	Neg.
W. D.	16	M.	0	1923	1923	B	1:160	1:160	S. C. A.	Neg.
F. K.	48	F.	1918	1923	1928	2	1:160	1:160	S. C. A.	Neg.
H. P.	41	F.	1926	0	1926	3	1:160	1:160	S. C. A.	Neg.
J. M.	43	M.	1918	1918	1928	3	1:80	1:160	S. C. A.	Neg.
H. K.	24	M.	0	1926	1926	1	1:160	1:40	S. C. A.	Neg.
D. S.	34	F.	1918	0	1928	1	1:320	1:180	S. C. A.	Neg.
G. H.	47	M.	0	0	1928	2	1:320	1:160	S. C. A.	Neg.
H. S.	52	M.	1918	0	1926	2	1:40	1:40	S. C. A.	Neg.
W. D.	18	F.	0	1929	1929	1	1:160	1:40	S. C. A.	Neg.
J. M.	26	M.	1918	1924	1924	3	1:160	1:80	S. C. A.	Neg.
F. G.	43	M.	0	0	1926	2	1:160	1:80	S. C. A.	Neg.
J. D.	30	F.	0	0	1925	1	1:160	1:160	S. C. A.	Neg.

(Graduate Hospital, University of Pennsylvania)

Name.	Age.	Sex.	Flu.	A. E.	C. E.	Park.	Agg.	Floc.	For. agg.	
I. D.	24	F.	1918	0	1923	3	1:20			
M. M.	58	M.	1918	0	1929	2	1:80	1:40	B. Mel.	Neg.
M. Z.	21	F.	1918	1918	1927	3	1:40			
E. F.	23	F.	1918	1921	1921	2	1:40			
W. R.	24	M.	0	1920	1926	1	1:80	1:80	S. Vir.	Neg.
R. S.	36	F.	1918	0	1929	3	1:160	1:40	S. Vir.	Neg.
L. S.	39	F.	0	1921	1923	3	1:20	1:20	S. C. A.	Neg.
T. C.	30	M.	0	0	1927	1	1:40	1:160	S. C. A.	Neg.
P. L.	29	M.	1929	0	1929	1	1:40	1:40	S. C. A.	Neg.
B. G.	32	F.	1918	0	1922	3	1:40	1:80	S. C. A.	Neg.
J. R.	29	M.	0	0	1925	2	1:160	1:80	S. C. A.	Neg.
H. J.	31	M.	0	0	1926	3	1:320	1:160	S. C. A.	Neg.
P. L.	13	M.	0	0	1929	1	1:40	1:40	S. C. A.	Neg.
R. Z.	35	M.	0	1923	1929	1	1:20	1:20	S. C. A.	Neg.

(Miscellaneous Cases)

N. D.	19	F.	0	1921	1921	4	1:160	1:80	S. Vir.	Neg.
M. L.	24	F.	0	1924	1925	1	1:80	1:80	S. Vir.	Neg.
M. M.	24	F.	1918	1920	1921	4	1:80	1:80	S. C. A.	Neg.
F. R.	49	M.	1918	1921	1921	1	1:80	1:80	S. C. A.	Neg.
S. S.	30	F.	0	1923	1929	1	1:80	1:80	S. C. A.	Neg.
J. W.	70	F.	1918	0	1924	1	1:320	1:80	S. C. A.	Neg.
J. M.	55	M.	1918	1921	1921	2	1:40	1:80	S. C. A.	1:20
A. F.	15	M.	1918	0	1928	2	1:40	1:20	S. C. A.	Neg.
E. B.	38	F.	0	1928	1928	2	1:80	1:40	S. C. A.	Neg.
H. G.	15	M.	1918	0	1926	B	1:160	1:80	S. C. A.	Neg.
M. S.	25	F.	0	1925	1925	1	1:20	1:40	S. C. A.	Neg.
A. R.	24	F.	1918	1925	1925	2	1:80	1:40	S. C. A.	Neg.
A. J.	32	M.	1918	1925	1925	4	1:320	1:80	S. C. A.	Neg.
L. E.	54	F.	1918	0	1928	1	1:40	1:20	S. C. A.	Neg.
M. C.			No data				1:80	1:80	S. C. A.	Neg.
A.			No data				1:40	1:40	S. C. A.	Neg.
T.			No data				1:160			

(Philadelphia General Hospital)

R. F.	25	M.	0	0	1923	2	1:40	1:80	S. Vir.	Neg.
F. D.	32	M.	1918	1921	1921	4	1:160			
A. S.	40	M.	0	1923	1924	2	1:80	1:40	S. C. A.	Neg.
S. A.	20	M.	0	1924	1926	4	1:40			
G. C.	38	M.	1920	1920	1924	2	1:80			
H. J.	21	M.	0	1923	1926	4	1:40			
C. P.	22	M.	0	1920	1922	4	1:40	1:40	S. C. A.	Neg.
C. D.	13	M.	0	1919	1921	4	1:320	1:40	S. C. A.	Neg.
C. B.	31	M.	0	0	1922	2	1:40	1:40	S. C. A.	Neg.
W. B.	36	M.	1918	0	1923	4	1:160	1:160	B. Mel.	Neg.
E. D.	43	M.	1921	1921	1926	1	1:80	1:80	S. C. A.	Neg.
A. D.	20	M.	0	1920	1920	4	1:20	1:20	S. C. A.	Neg.
J. F.	24	M.	0	1923	1923	4	1:160	1:60	B. Mel.	Neg.
R. G.	48	M.	1918	0	1928	2	1:80	1:40	S. C. A.	Neg.
G. H.	62	M.	0	1926	1926	2	1:80	1:160	S. C. A.	Neg.
S. T.	24	M.	1918	1921	1921	2	1:160	1:80	S. C. A.	Neg.
G. M.	60	M.	0	0	1918	3	1:40			
M. L.	78	M.	1918	0	1920	3	1:160	1:80	B. Mel.	Neg.

TABLE I.—AGGLUTINATION AND FLOCCULATION REACTIONS IN CHRONIC EPIDEMIC ENCEPHALITIS. (PFEIFFER BACILLUS WAS FOUND IN NASOPHARYNGEAL CULTURES OF ALL CASES.)—(Continued)

(Philadelphia General Hospital—Continued)

Name.	Age.	Sex.	Flu.	A. E.	C. E.	Park.	Agg.	Floc.	For. agg.	
P. M.	40	M.	0	1926	1928	2	1:80	1:80	S. C. A.	Neg.
A. P.	35	M.	1924	1924	1926	2	1:80	1:80	B. Mel.	Neg.
J. P.	60	M.	0	0	1924	2	1:160	1:80	B. Mel.	Neg.
H. S.	45	M.	1918	1918	1924	4	1:40	1:40	S. C. A.	Neg.
J. T.	51	M.	0	0	1925	2	1:40	1:40	S. C. A.	Neg.
H. E.	24	M.	1918	0	1928	2	1:160	1:80	S. Vir.	Neg.
J. V.	61	M.	0	0	1928	1	1:80	1:80	S. C. A.	Neg.
R. J.	24	M.	0	1929	1929	1	1:20	1:40	S. C. A.	Neg.
C. B.	32	M.	0	0	1928	1	1:160	1:80	S. C. A.	Neg.
A. W.	18	M.	0	1923	1923	2	1:80	1:80	S. C. A.	Neg.
M. K.	45	M.	1918	0	1924	3	1:160	1:80	S. C. A.	Neg.
C. K.	45	M.	0	1924	1927	1	1:80	1:40	S. C. A.	Neg.
P. S.	24	M.	0	1923	1923	2	1:160	1:80	S. C. A.	Neg.
J. M.	25	M.	0	1922	1925	3	1:160	1:40	S. C. A.	Neg.
M. P.	45	M.	0	0	1927	1	1:80	1:160	S. C. A.	Neg.
A. R.	22	M.	1918	0	1927	1	1:40	1:20	S. C. A.	Neg.
J. E.	24	M.	1918	0	1926	2	1:40	1:40	S. C. A.	Neg.
S. S.	55	M.	0	0	1925	2	1:40	1:40	S. C. A.	Neg.
A. F.	28	F.	0	1920	1924	3	1:20			
M. J.	36	F.	0	1921	1924	3	1:640			
A. S.	29	F.	1923	0	1923	2	1:80			
M. B.	48	F.	1921	0	1927	2	1:40			
E. S.	20	F.	1918	1924	1924	3	1:40	1:20	S. Vir.	Neg.
D. E.	31	F.	0	1921	1921	2	1:40	1:80	S. Vir.	Neg.
H. D.	32	F.	0	1923	1923	3	1:20	1:20	S. Vir.	Neg.
M. M.	28	F.	1918	1920	1920	3	1:80	1:40	S. Vir.	Neg.
H. S.	24	F.	1918	1924	1925	2	1:80	1:80	S. Vir.	Neg.
E. P.	19	F.	1918	0	1921	4	1:40	1:80	S. Vir.	Neg.
N. R.	38	F.	0	1923	1926	3	1:40	1:40	S. Vir.	Neg.
J. F.	57	F.	0	0	1924	2	1:80	1:80	S. Vir.	Neg.
M. K.	52	F.	0	0	1920	2	1:160	1:80	S. Vir.	Neg.
F. K.	41	F.	0	0	1921	3	1:80	1:80	S. Vir.	Neg.
S. E.	43	F.	1918	1923	1923	4	1:40	1:40	S. Vir.	Neg.
E. F.	27	F.	1918	0	1921	2	1:80	1:80	S. C. A.	Neg.
S. D.	68	F.	0	0	1920	4	1:160	1:80	S. C. A.	Neg.
R. T.	62	F.	0	0	1928	1	1:80	1:160	S. C. A.	Neg.
E. B.	35	F.	1918	0	1925	3	1:80	1:80	S. C. A.	Neg.
J. E.	61	F.	0	0	1928	4	1:40	1:80	S. C. A.	Neg.
N. H.	50	F.	1918	0	1928	1	1:80	1:80	S. C. A.	Neg.
M. F.	29	F.	0	1919	1927	2	1:80	1:20	S. C. A.	Neg.
L. S.	26	F.	1918	0	1926	1	1:40	1:80	S. C. A.	Neg.
J. S.	15	F.	0	1925	1925	1	1:80	1:80	S. C. A.	Neg.
C. L.	16	F.	0	1925	1928	1	1:160	1:80	S. C. A.	Neg.
A. P.	23	F.	0	0	1923	2	1:80	1:80	S. C. A.	Neg.
G. H.	30	F.	1918	1924	1925	2	1:40	1:20	S. C. A.	Neg.
J. M.	25	F.	1918	0	1925	1	1:40	1:40	S. C. A.	Neg.
A. C.	55	F.	1924	1924	1924	3	1:80	1:80	S. C. A.	Neg.
M. S.	26	F.	0	0	1928	3	1:80	1:80	S. C. A.	Neg.
F. A.	21	F.	1918	0	1929	1	1:80	1:80	S. C. A.	Neg.
M. M.	24	F.	0	1923	1926	2	1:320	1:160	S. C. A.	Neg.
A. G.	42	F.	0	0	1925	3	1:160	1:80	S. C. A.	Neg.
M. C.	28	F.	1918	1925	1925	1	1:80	1:80	S. C. A.	Neg.
A. H.	40	F.	1918	1919	1919	2	1:160	1:160	S. C. A.	Neg.
C. F.	20	F.	1918	1925	1928	1	1:80	1:40	S. C. A.	Neg.
A. J.	30	M.	0	0	1926	1	1:80	1:40	S. C. A.	Neg.
H. S.	70	M.	0	1920	1920	4	1:320	1:160	S. C. A.	Neg.
M. K.	24	M.	1918	0	1918	2	1:40	1:40	B. Mel.	Neg.

Of 122 control cases only 3 afebrile cases showed agglutinations with the Pfeiffer bacillus. One was a patient with central nervous system syphilis (1 to 80); another a patient diagnosed lenticular degeneration whose symptoms—choreiform movements—dated from 1912, when at the age of one year, he had an undiagnosed febrile condition followed by great restlessness (1 to 40); and the third, a patient suffering from bronchiectasis and asthma from whom the Pfeiffer bacillus was constantly obtained in bronchial cultures (1 to 20). A recovered case of influenzal meningitis did not agglutinate, but showed flocculation with the Pfeiffer bacillus.

Four cases with marked hyperpyrexia also agglutinated the Pfeiffer bacillus in titers of 1 to 20 to 1 to 80. One of these cases also agglutinated *Bacillus melitensis abortus*, one *Anhemolytic streptococcus* and 2 *Bacillus typhosus*. The other 110 cases gave negative agglutination and flocculation reactions with the Hammett strain of the Pfeiffer bacillus. Of 10 undiagnosed patients examined for Dr. F. Burge of Philadelphia, 4 gave positive agglutinations and 6 negative reactions. These cases have not been listed as they cannot be classified.

In further culture studies the Pfeiffer bacillus was isolated from the throats of chronic encephalitic patients in pure culture. Antigens were made from these strains by the method before described. In 18 cases the strain of Pfeiffer bacillus isolated from the patient's nasopharynx was agglutinated by the homologous serum in dilutions from 1 to 40 to 1 to 2560. The titers of the homologous agglutinations were higher than when the Hammett antigen was used against the same sera. These 18 encephalitic antigens were also agglutinated by the Hammett immune horse serum: the agglutination titers thus obtained ranging from 1 to 40 up to 1 to 2560. Not in all cases was the agglutination with the Hammett immune serum as high as that with the homologous serum, but there was an indication of subgrouping serologically. Further work will be carried out upon this particular phase of the problem as it appears most suggestive.

Experimental work with animals is contemplated in order to determine whether or not there is a serologic relationship among the strains of Pfeiffer bacillus isolated from patients suffering with chronic epidemic encephalitis. Another group of animals will be sensitized to these same strains in order to determine whether there is a protein common to these strains.

Treatment. At the present time 62 patients suffering with chronic epidemic encephalitis are being treated with the bacteriologic products of the Hammett strain of the Pfeiffer bacillus. These products are the immune horse serum, the soluble antigen and the vaccine.

The horse serum is prepared by immunizing the animal against the Hammett strain of the Pfeiffer bacillus. The vaccine is made

in the usual manner but the organisms killed with thymol. The following technique is used in the preparation of the soluble antigen. Cultures of the Hammett strain of the Pfeiffer bacillus are streaked on brown-blood plates and incubated overnight at 37.5° C.; the resulting growth is washed from the plates with sterile physiologic salt solution and the heavy particles allowed to settle to the bottom of the tube. Two washings are made of the supernatant fluid. The organisms are heat killed at 60° C. for one hour and resuspended in a dilution of one hundred million organisms per cubic centimeter and allowed to stand at icebox temperature for one week. This suspension is then passed through a Grade A Berkefeld filter, and tested for sterility. The resulting water-clear filtrate is then diluted 1 to 10,000 for clinical use. This method is very similar to the one used by J. C. Small in his preparation of the soluble S.C.A. antigen, the only difference being in the original method of growth and treatment of the organisms.

We feel justified in using a soluble antigen of a virulent strain of Pfeiffer bacillus in the treatment of these cases, since it has been found by mouse experimentation that toxins from virulent strains of the Pfeiffer bacillus although of dissimilar serologic relationship, were neutralized by the same immune antiserum. This work will be further discussed in a future paper. This observation finds a parallelism in diphtheria toxins where, although there are several serologic strains, all are neutralized by the same antitoxin. It is upon this basis that we use the Hammett soluble antigen, for although it was not isolated from a case of chronic encephalitis, it is a most virulent strain.

Sixteen cases were treated with the immune serum. Of these 7 showed serum reactions with fever and urticaria. There was some improvement in approximately one-third of these cases but this is not sufficient to claim specificity. It could well have been the result of nonspecific protein reaction.

Since the patients treated with soluble antigen showed as much improvement as those treated with serum and antigen and more than those treated with serum alone, the use of the serum has been discontinued in chronic manifestations of the disease, these cases being treated with the soluble antigen.

It has been found that 0.1 cc. of a 1 to 10,000 dilution of the soluble antigen every five to seven days gives best results. Improvement under this treatment consists in reduction of the extrapyramidal rigidity which, is the most constant finding in this disease and is the cause of its most important symptoms and signs. The patient gradually feels less stiff, regains the use of his arms and legs, the posture becomes more erect, there is a decrease in festination, the face becomes more mobile and the speech less monotonous. The first symptom of improvement noted in early cases of this disease is decrease in slowness. It is an interesting observation that as the

extrapyramidal rigidity decreases, tremor concomitantly increases. This can be explained upon a purely mechanical basis.

Increasing doses of the soluble antigen aggravate rather than relieve the symptoms. There is however no febrile reaction. In one patient who showed decrease in rigidity with repeated doses of 0.1 cc. of 1 to 10,000 dilution of the antigen, the dose was increased to 0.4 cc. Her rigidity was increased by this dose to such an extent that she could hardly return to clinic. This phenomenon has been repeated in several instances.

But little improvement is noted in less than one month of treatment. Therefore we shall report only those cases which have been treated for this period or longer. Of these there are 46 cases, 34 of which show definite improvement. Of the patients with Parkinson's syndrome 78 per cent have shown a definite decrease in extrapyramidal rigidity. Subjectively there is a sense of greater mobility and the patient is able to get about better than before. It is most difficult to determine improvement in behavior cases. The environment of these patients has not been sufficiently controlled to make such observations valid.

We have been forced to give hyoscin and stramonium to about 20 per cent of our cases to enable them to get to the clinic. Our technique has been to allow our patients to continue with the same dosage of drugs that they were taking before they received their first dose of soluble antigen. This dose is then reduced as the antigen treatment progresses. Several patients who were taking $\frac{1}{100}$ gr. of hyoscin three times daily have had this drug entirely withdrawn and now are better than they were while taking it.

We expect to treat an adequately controlled series of cases of chronic epidemic encephalitis with this soluble antigen on the wards. Our results then will not be vitiated by the use of drugs. We also intend to treat a series of controls with the same dosage of the soluble antigens of other organisms.

It is logical to believe that there is a focus of infection in these cases. Since the Pfeiffer bacillus is invariably isolated from nasopharyngeal cultures, the upper respiratory tracts of these patients are being carefully investigated. Thus far 20 of our cases have had both Roentgen ray studies of the accessory sinuses of the nose, and examination by a laryngologist. Eighteen cases show evidence of definite sinus involvement either by Roentgen ray or clinical examination. Of these, 13 cases have disease of the ethmoids. Deflected septum with blocking of the nasal passage is a common finding and cultures of the middle meatus of the nose reveal the presence of the Pfeiffer bacillus in 80 per cent of such cases.

A group of these patients will be treated with a course of Pfeiffer vaccine and local application of Besredka filtrate along with any mechanical interference indicated to clear up the sinuses.

The fact that the patients improve on constant minute doses of

the soluble antigen, however, suggests that we are dealing also with a sensitization. There is need for further investigation along these lines. We consider however that our results are not due to nonspecific protein reaction, since the usual dose of antigen contains only .000,000,000,094 gr. of protein.

Summary. 1. The Pfeiffer bacillus was isolated from nasopharyngeal cultures of chronic encephalitic patients in 100 per cent of cases.

2. The sera of chronic encephalitic patients agglutinated the Hammett strain of the Pfeiffer bacillus in 100 per cent of cases studied. Flocculation tests were also invariably positive with these sera. No other organism thus far tested has been consistently agglutinated by chronic encephalitic sera.

3. Cultures of the Pfeiffer bacillus isolated from 18 cases of chronic encephalitics agglutinated their respective patients' sera and also agglutinated the Hammett strain of Pfeiffer bacillus immune serum. The agglutination with the Hammett immune sera was not so high as that of the homologous patient's sera but suggested the existence of a serologic subgrouping.

4. Of the control series: (a) Pfeiffer bacillus was isolated in 46 per cent of nasopharyngeal cultures; (b) 122 nonencephalitic sera were tested for agglutination. Of these, 114 neither agglutinated nor flocculated the Pfeiffer bacillus.

Of the 7 control cases that agglutinated the Pfeiffer bacillus 3, were afebrile, a case of syphilis of the central nervous system, a lenticular degeneration with a questionable history and a patient proved to be sensitive to the Pfeiffer bacillus. Four febrile cases agglutinated the Pfeiffer bacillus but also agglutinated other organisms.

5. Of 20 cases of chronic encephalitic Parkinsonism studied for sinus disease, 18 gave positive findings either by Roentgen ray or clinical examination; 13 of these had definite disease of the ethmoids.

6. Of 46 cases of chronic encephalitic Parkinson's disease treated for one month or more with the soluble antigen, 78 per cent show improvement. This is considered as not due to a nonspecific protein reaction, since the dose of antigen given contains only ninety-four ten-billionths of a gram (.000,000,000,094) of protein.

NOTE.—We wish to extend our thanks to the neurologists at the Hospital of the University of Pennsylvania, the Philadelphia General, the Graduate and Episcopal Hospitals for permitting us to study their patients and to Dr. A. S. W. Rosenbach, whose generosity has furthered this work.

REFERENCES.

1. Epidemic Encephalitis. Report of a Survey of the Matheson Commission, Columbia University Press, 1929.
2. Evans, M. J., and Small, J. C.: A Study of Agglutinable Antigens of Bacillus Influenzæ, *J. Immunol.*, 1925, 10, 613.
3. Evans, M. J.: A Study of Hemophilus Influenzæ, *Am. J. Med. Sci.*, 1930, 79, 177.

THE FUTILITY OF ALKALI TREATMENT IN DIABETIC COMA.

ANALYSIS OF FORTY-SEVEN CASES.*

By I. I. LEMANN, M.D.,

PROFESSOR OF CLINICAL MEDICINE, TULANE UNIVERSITY; CHIEF OF MEDICAL SERVICE,
TOURO INFIRMARY, NEW ORLEANS, LA.

THE present series is presented as corroborative evidence in support of Joslin's contention that the use of alkalies in diabetic coma is unnecessary. While his experience in a series of 105 cases is convincing, it seems desirable to gather as large a number of coma cases treated without alkalies and as from as many sources as possible. In spite of the flood of papers concerning insulin in the past seven years, there are relatively few recorded series of coma cases from which conclusions may be drawn. Table I gives all such series with more than 20 cases.

While Joslin¹ enumerates Petren, the Minkowski school, Faltz, Priesel and Wagner, Newburgh and Marsh, Bertnard Smith and many others as having given up the use of alkalies, there still remains an uneasy feeling in the minds of many that the antiketogenic effect of insulin may not be sufficient nor prompt enough and that its effect upon the alkali reserve may be inadequate to offset the acidosis caused by other possible acid bodies. I have recently had an opportunity to review the records of 49 cases of coma treated by a number of different men in a certain hospital in the past five years. In 25 of these alkalies had been used. Meyer-Bisch² in 1926, in attributing the symptoms of diabetic coma to concentration of the blood and to hypochloremia, reported 4 cases of coma in which the intravenous injection of soda bicarbonate solution restored the patients to consciousness within a few minutes, whereas the coma had continued after insulin (in one case where the blood sugar had fallen to 80 mg. per 100 cc. and where "hypoglycemic twitchings" had appeared). Hédon³ reported that his depancreatized dog brought into diabetic coma by the sudden withdrawal of insulin was restored instantly to consciousness by intravenous soda bicarbonate solution whereas the reinauguration of insulin therapy caused the disappearance of the glycosuria, hyperglycemia and diaceturia but had not brought about the restoration of consciousness. Such experiences might serve to reinforce the feeling of some that soda bicarbonate should supplement the effect of insulin. The suggestion of Bock⁴ and Starr and Fitz⁵ that there may be acting in coma, acid bodies other than ketone bodies is held to be an additional reason for the employment of alkalies. In this connection we may ask, Do the

* Read at the meeting of the Association of American Physicians Atlantic City, May 7, 1930.

ketone bodies act as specific poisons or merely as any other acids might? The question of the pathogenesis of diabetic coma has not been solved in spite of the long controversy and of the numerous researches.

TABLE I.—SERIES OF COMAS REPORTED IN LITERATURE DURING INSULIN ERA.

Author.	Cases of coma.	No. of deaths.	Died (%).	Year.	Remarks.
1. Foster: J. Am. Med. Assn., 84, 719	20	2	10	1925	No statement as to use of alkalies.
2. Kahn and Olmsted: J. Met. Res., 7, 29	24	3	12.5	1925	All deaths in cases with complications. Total series, 25; 1 omitted because death due to no insulin being available. Soda was used.
3. Violin: Wien. klin. Wchnschr., 39, 1304	21	5	24	1926	No statement as to use of alkalies.
4. Leake: Calif. and West. Med., 26, 475	53	37	70	1927	27 had grave complications. Soda used.
5. Chabanier, <i>et al.</i> : Presse méd., 1, 83	28	2	7.1	1927	No soda.
6. Petren: Verhand. d. deutsch. Kong. f. inn. Med., 39, 203	72	4.1*	5.5	1927	* Including 1 death apparently from pneumonia. No soda.
7. Elias: Wien. med. Fakult, No. 95 . .	42	..	24	1924-1925	Quoted by H. J. John.
8. John, H. J.: J. Am. Med. Assn., 93, 425	71	4	5.6	1929	Insignificant quantities of Bisodol used by mouth.
9. Joslin, E. P.: Med. Clin. N. Am., 13, 11	105	7	6.6	1929	7 deaths during coma, 2 from uncomplicated coma, 5 from complications with coma; 7 more recovered from coma but died in hospital from complications in from 6 to 31 days. No alkalies used
10. Blackfan	21	0	0	1929	Quoted by Joslin (9); 1 patient received alkalies.
11. Lemann: Present series	47	5	10.6	1930	2 deaths within 2 hours of admission; 1 death with complicating chronic nephritis.
12. Lemann: Present series; cases without alkali	41	3	7.3	1930	If 2 patients who died within 2 hours are omitted, net mortality is 2.4 per cent.

It is striking that insulin acts not only as a specific antidote to the ketone bodies but also by raising the soda bicarbonate content of the blood and tissues sometimes even to the point of causing a

definite and menacing alkalosis; so that whether we adopt the acid intoxication theory or the specific intoxication theory, insulin might be by itself theoretically regarded as sufficient. The argument in favor of insulin without reinforcement of alkalis is strengthened not only by the consideration of its production of alkalosis but also by its action in those cases of diabetic coma without the appearance of ketonuria. In these latter cases the failure of the ketone bodies to appear in the urine has been attributed to kidney block caused either by the coma, or rather its specific cause, or by a concomitant or previously existing nephritis. In such cases, therefore, we are dealing not only with the acidotic or specific effect of the ketone bodies but also with the effect of other acidotic material retained in the body because of the inability of the damaged kidney to excrete it. The effect of insulin, therefore, in rescuing such diabetic-coma patients who do not exhibit ketonuria is additional evidence of its adequacy even where we have to concede the theoretic need of combating acidosis arising from sources other than the ketone bodies. I have previously⁶ reported the details of the rescue of such patients with insulin only and these cases are included in the present series.

The relation of the degree of the impairment of the alkali reserve to the depth of the coma is of interest and perhaps importance in considering the rôle of alkali therapy. I have found, like Joslin, that the degree of coma is not proportional to the blood CO_2 level. The most profound coma was not always characterized by the lowest CO_2 combining power of the blood plasma nor on the other hand was the lowest CO_2 value accompanied by the deepest coma. Should this be regarded as evidence against the acid intoxication theory and in favor of the specific ketone intoxication theory of the pathogenesis of diabetic coma? I have observed recovery from coma usually running parallel to the rise in the CO_2 combining power of the blood plasma and the disappearance of the ketonuria. This is apparently not in accordance with Joslin's experience.⁷

The present report covers 47 comas in 34 patients. Not all of these patients were completely unconscious. Some of those retaining consciousness to a certain degree at least exhibited, as I have said, the lowest CO_2 combining power. Where complete coma was not present, the diagnosis of "diabetic coma" was justified on the basis of the Kussmaul air hunger, the clouded sensorium and the low CO_2 combining power. The lowest CO_2 combining power was 6.6 volume per cent. The highest blood-sugar reading was 1204 mg. per 100 cc. Both of these patients were rescued. Included in this series also are 2 patients whose urine showed no diacetic acid at the time of the coma. One of these patients had congestive heart failure, showed auricular fibrillation at the time of her coma and subsequently died of heart and kidney disease many months after the diabetic coma. The other patient proved also to have evidence of chronic kidney disease. I saw her first when she had been completely unconscious for more than twelve hours. Intravenous infusion of

soda bicarbonate by her attending physician twelve hours before my first visit had produced no effect whatsoever. She was rescued then by insulin alone and without further alkalies. In a second coma she was again rescued without alkalies. In the third coma, in which she died, soda bicarbonate intravenously was again used in addition to the insulin but without affecting the clinical picture. Unfortunately no autopsy was permitted. The experience in the four comas seen in these 2 patients would lead one to believe that insulin alone and without alkalies is effective and adequate to combat the acidosis caused by hypothetic other acid bodies when chronic kidney disease exists as a complication of diabetes.

Allusion may also be made here to the acute kidney block produced apparently by the diabetic coma itself. In the case for example of the patient with the blood sugar of 1204 mg. per 100 cc. there was much evidence of such a condition. The urine showed many hyaline, granular and finely granular casts, red blood cells and pus cells. The relation of the kidney block to the level of the blood chemistry and to the CO_2 combining power is shown in Table II. It will be noted that the retention of nitrogen persisted after the patient had been restored to consciousness and the CO_2 combining power approached normal. At the end of the first month the total nonprotein nitrogen of the blood was 30 mg. per 100 cc. and there was no evidence of any nephritis. It is common to find that all the evidences of severe nephritis clear up when the patient recovers from the diabetic coma. The point to be made here again is that insulin alone is sufficient to combat such hypothetic acidosis as may be attributed to the acute kidney involvement and not regarded as essentially diabetic (ketogenic).

TABLE II.—RELATION OF KIDNEY BLOCK TO THE LEVEL OF BLOOD CHEMISTRY AND TO THE CO_2 COMBINING POWER.

Blood sugar.	Total non-protein nitrogen.	Creatinin.	Uric acid.	CO_2 combining power.	Remarks.
1204	60	3.11	8	9	
500	75	3	10	31	380 units of insulin to this point—end of first 24 hours.
325	100	3.11	8.8	37.4	End of second 24 hours.
258	100	3	8	36.5	End of third 24 hours.
103	88.8	2.3	6.64		End of fifth 24 hours.

The 47 comas in the 34 patients were complicated by serious conditions in 14 comas.

1. Abscess of the gluteal region. Patient recovered. No. 3033.
2. Abscess of the gluteal region, tuberculosis of the breast. Patient recovered. No. 2898.
3. Perirectal abscess. Patient recovered. No. 1953.
4. Otitis media. Patient recovered. No. 1972.

5. Otitis media. Patient recovered. No. 2898.
6. Organic heart and kidney disease. Patient recovered. No. 2374.
- 7, 8, 9. Chronic kidney disease. Patient recovered from the first and second comas but died in the third. No. 2021.
10. Pyelonephritis. Patient recovered. No. 2367.
11. Septicemia, bronchopneumonia and pyelonephritis. Patient recovered from the coma but died nearly a month later from the septicemia and pyelonephritis. No. 1898.
12. Alveolar abscess. Patient recovered. No. 3035.
13. Multiple large carbuncles. Patient recovered. No. 2146.
14. Large carbuncle of the neck. Patient died within two hours of admission. No. 2389.

It will be observed, therefore, that serious complications and infections did not produce an acidosis which could not be successfully combated with insulin alone and without alkalies.

The age of the patients was below ten years in 3 comas, between ten and twenty years in 16 comas and over twenty years in 28 comas.

There were 5 deaths in this series of 47 comas—a mortality of a little more than 10 per cent. Two patients died within two hours of their admission. One of the other deaths was certainly due to insufficient insulin; it occurred in the early insulin days, before an adequate supply was available. Another death was possibly due also to insufficient insulin for I would now consider the amount used (150 units in fifteen hours) inadequate. Soda bicarbonate was used in only 6 instances—all in the early insulin days and always in very small amounts—4 gm. (200 cc. of 2 per cent solution). One of the 6 instances is represented by the patient who died because of inadequate supply of insulin. Two other instances were represented by the first and third comas of the patient with chronic nephritis without ketonuria.

Forty-one comas, therefore, were treated with insulin alone without alkali. In this consecutive series there were 3 deaths, namely, 2 patients who died within two hours of their admission and the patient who received 150 units of insulin in fifteen hours. If we omit the 2 patients dying within two hours of their admission we have one death in 41 comas or a net mortality of 2.4 per cent, even in the presence of grave complications.

The case against alkalies can, therefore, be stated exactly as Joslin has put it—first, they are unnecessary, second, they may do harm. It is hardly necessary to refer to the futility of alkalies alone before the insulin era. As Olav Hanssen⁸ has written “the coma patients who have been rescued by this treatment are so few that their number can certainly be written down in single numerals.” St. Lorant⁹ saved one out of 42 coma cases in the preinsulin era. The one was saved by rupture of the ear drum relieving an acute middle-ear abscess. All the others had had great quantities of alkalies. Hanssen found that in 3 out of 6 cases treated with intravenous injections of sodium bicarbonate solutions convulsions occurred. In the postmortem examinations of the brains in all of

the patients treated with sodium bicarbonate there was found intense hyperemia and edema in the thin meninges. In 5 cases there were small flakelike hemorrhages in the meninges and in 2 cases there were small hemorrhages in the brain substance. Even those who at first advocated the use of soda bicarbonate intravenously as an adjunct to insulin therapy in coma have retreated and agree that¹⁰ "undoubtedly too much alkali will kill and undoubtedly alkali intravenously administered is exceedingly dangerous and should rarely be employed even by those highly skilled in its administration." Some still contend that soda bicarbonate in amounts of 20 to 30 gm. is a useful addition to the treatment of diabetic coma. The usefulness of these small doses may be questioned in the light of the calculation that from 100 to 200 gm. would be required to neutralize the amount of the ketone bodies found in the urine of coma patients.⁸ Why give any if insufficient amounts are given and if it can be shown that none is needed? Recent literature contains reports of alkalosis caused by therapeutic doses of alkali in the treatment of gastric and duodenal ulcer.¹¹ With even small amounts given by mouth or rectum care must "be exercised that the alkali concentration of a liquid does not cause its rejection."¹⁰ This caution is by no means based on theoretical considerations. The retention of fluids by the desiccated coma patients is of much greater importance than any questionable good of small doses of alkali.

Conclusion. No indication nor excuse for the use of alkali therapy to supplement insulin was found in the depth of the coma, in duration before the institution of treatment, in the maximum grade of glycemia, the lowest value of CO_2 combining power of the blood plasma, in grave complications, nor in kidney block nor concomitant chronic nephritis. Soda can do no good and can do harm.

REFERENCES.

1. Joslin, E. P.: *Treatment of Diabetes Mellitus*, 4th ed., p. 668, Lea & Febiger.
2. Meyer-Bisch, Robert; and Wohlenberg, Willi: Investigation on Mineral in Diabetes; Change of Salts and Sodium Chlorid Metabolism in Diabetic Coma; Justification of Alkali Treatment, *Ztschr. f. klin. Med.*, 1926, 103, 260; *Abst. J. Am. Med. Assn.*, 1926, 87, 211.
3. Hédon, E.: Acidosis and Diabetic Coma in the Depancreatized Dog, *Compt. rend. Soc. de biol.*, 1925, 93, 89.
4. Bock, A. V., Field, H., Jr., and Adair, G. S.: Acid-base Equilibrium in Diabetic Coma—Being a Study of Five Cases Treated with Insulin, *Jour. Metab. Res.*, 1923, 4, 27.
5. Starr, P., and Fitz, R.: Excretion of Organic Acids in Urine of Patients with Diabetes Mellitus, *Arch. Int. Med.*, 1924, 33, 97.
6. Lemann, I. I.: Pitfalls in the Diagnosis of Diabetic Coma, *Med. Clin. North America*, 1926, 9, 959.
7. Joslin, E. P.: *Treatment of Diabetes Mellitus*, 4th ed., p. 653, Lea & Febiger.
8. Hanssen, Olav: On Some Effects of Large Doses of Soda Bicarbonate in Diabetes Mellitus, *Ztschr. f. klin. Med.*, 1912, 76, 219.
9. St. Lorient: On the Question of the Cause of Diabetic Coma, *Klin. Wchnschr.*, 1926, 5, 216.
10. Campbell, W.: Acidosis, Coma and Infections in Diabetes Mellitus, *Intern. Clin.*, 36th series, 1926, 4, 3.
11. Hardt, L. L., and Rives, A. B.: Toxic Manifestations Following Alkaline Treatment of Peptic Ulcer, *Arch. Int. Med.*, 1923, 31, 171.

REVIEWS.

SURGERY OF THE LUNG AND PLEURA. By H. MORRISTON DAVIES, M.A., M.D., M.CH. (CANTAB.), F.R.C.S. (ENGLAND). Pp. 355; 104 illustrations. New York: Oxford University Press, 1930.

THERE has been a most noticeable advance in the surgery of the chest during the last ten years. Sauerbruch, in Germany, and Lilienthal, in America, have given excellent treatises on intrathoracic surgery, but this present work compares most favorably with theirs. The writer has drawn freely on the literature as well as his own experience, which latter has been most extensive. This is especially true of the chapters on tuberculosis, which are valuable alike for their diagnostic acumen and their surgical wisdom, because of the writer's past experience and long training in sanatorium work. The entire subject is covered. Chapters deal fully with the anatomy, physiology, diagnosis, pathology and treatment of disease and injury of the thorax and its contents. The text is supplemented by numerous well-chosen and excellently reproduced illustrations, chiefly drawn from the writer's own case histories. A very full bibliography is added as a last chapter of this most instructive and up-to-date contribution.

E. E.

THE HARVEY LECTURES, SERIES XXIV, 1928-1929. Pp. 216; 36 illustrations. Baltimore: The Williams & Wilkins Company, 1930.

THE Harvey Lectures for 1928-1929 maintain their customary high level. The following lectures were given: "Senescence and Rejuvenescence from a Biologic Standpoint," by C. M. Child; "The Nature of the Ultrafilterable Viruses," by F. d'Herelle; "The Metallotherapy of the Spirochætososes," by C. Levaditi; "Urine Formation During the Acute and Chronic Nephritis Induced by Uranium Nitrate," by William de B. MacNider; "Constitutional Variation and Susceptibility to Disease," by Wade H. Brown; "Calcium and Phosphorus Metabolism," by Joseph C. Aub; "The Biochemical Digitalis Problems," by Walther Straub; "The Pathogenesis and Transmission of Tuberculosis," by Eugene L. Opie.

E. K.

PEPTIC ULCER. By JACOB BUCKSTEIN, M.D. Vol. X of *Annals of Roentgenology*. Edited by JAMES T. CASE, M.D. Pp. 337; 287 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$12.00.

THIS monograph is one of the series of annals published by Paul B. Hoeber, and it deals with the roentgenologic aspects of peptic ulcer. The author has briefly considered the types of stomachs, and the various types of gastric mucosa. He also discusses briefly the various types of ulcers of the stomach and duodenum, and he includes two illustrations of ulcers of the esophagus. The pathology of the lesions found at operation are correlated with the roentgenologic findings. Included is some excellent work on the roentgenographic findings of ruptured peptic ulcers, jejunal ulcers and gastrocolic fistulas resulting from marginal ulcers.

The subject is presented in a concrete and excellent manner. The print and illustrations are excellent. The roentgenologic findings are correlated with the operative and pathologic findings, and this makes the book more valuable. It should be of interest to all roentgenologists.

E. P.

THE TREATMENT OF SKIN DISEASES IN DETAIL. By NOXON TOOMEY, M.D. Pp. 512. St. Louis: The Lister Medical Press, 1930. Price, \$7.50.

THIS is apparently the third volume of a system, of which the first two volumes are yet to appear. Like all texts dealing with dermatologic subjects, it presents features both to admire and condemn. The book is without illustrations, which is an interesting departure, and contains valuable detail as to the makeup and application of medicinal preparations which is frequently omitted from the average practitioners' handbook. The attempt to reclassify certain aspects of dermatology results in the addition of a number of new, not particularly useful and rather cumbersome names to an already overloaded nomenclature. A genuine effort is made to present the constitutional background of certain dermatoses but the product still retains the unmistakable flavor of empiricism that continues to mark even the best dermatologic practice. Considering that dermatology differentiates itself sharply into procedure which should be available to the practitioner and procedure which he should never attempt, it is probably too much to expect that any inclusive text will ever wholly satisfy both groups. It is noticeable that the author subscribes to the use of Roentgen ray in the removal of excessive hair growth, a procedure which, no matter how carefully guarded technically, does not have the general acceptance of dermatologists either in this country or abroad. On the

other hand, the book contains items of detail of the greatest interest to the practising dermatologist. For example, this is the only text in which the Reviewer has noted sufficient attention to the question of qualified results in hair removal and the only one emphasizing a genuine knowledge of dietotherapy. One turns from the work with a feeling that this is a very creditable effort to bring dermatologic practice down to the detail which is of its essence, but that it has not yet accomplished what another generation may do for us—the adequate textbook presentation of a rational dermatologic treatment.

J. S.

TONSIL SURGERY. By ROBERT H. FOWLER, M.D. Pp. 288; 103 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$10.00.

AUGMENTED by splendid illustrations, this book describes in great detail the anatomy and surgery of the faucial tonsil. The details of the technique of the tonsil operation as carried out in eight different clinics, are presented. The author and coworkers deserve particular praise for their original work on the anatomy of this region. It is unfortunate that one of the methods advocates the injection of cocain solution for the purpose of local anesthesia (page 104). In the present era of safer local anesthesia it seems dangerous to present the above procedure as representative, for certainly almost all surgeons agree that under no circumstances should cocain be injected. With the above reservation, this book is recommended to the throat surgeon, especially the young man who wishes to crystallize his ideas and develop his technique for thorough, yet safe, tonsil surgery.

K. H.

TRAUMA, DISEASE, COMPENSATION. By A. J. FRASER, M.D. Pp. 524. Philadelphia: F. A. Davis Company, 1930. Price, \$6.50.

THE author has made a study of Workmen's Compensation and has here set down a compilation of cases and facts which may be used by those dealing in compensation and industrial insurance. The first chapter concerns the basis and scope of Workmen's Compensation and cases are cited defining the various provisions of the act. Various parts of the body are then discussed in detail and examples and authorities are given to show how the diseases under discussion may or may not be compensable. The chapters on fracture and hernia are good but the author has avoided one of the commonest industrial diseases, traumatic backache.

The book is evidently intended for use by the laity since a glossary is attached. Because the author is a Canadian a greater part of the authorities quoted and the opinions given come from British or Canadian literature, and some of the cases may not be applicable for use in the United States. However, it should prove useful to those dealing with compensation insurance and industrial medicine.

L. F.

DIE REGULIERUNG DES BLUTKREISLAUFES. By DR. W. R. HESS. Pp. 163; 21 illustrations. Leipzig: Georg Thieme, 1930. Price, M. 12.

THE author has succeeded in the stupendous task of covering the extremely large literature on this subject with great thoroughness. A list of 703 references are given even though prolific writers are usually referred to through review articles or books (for example, T. Lewis is cited in a single reference only). The monograph will consequently prove of very great value to all workers in this and related subjects. Often 20 to 40 references are made in the course of a single page; this increases the value of the book as a guide to the study of the literature, but prevents to some extent the development of the material discussed in any detail in the monograph itself.

The author has succeeded surprisingly well in keeping the references up to date and many references to articles published in 1929 are included.

The subjects dealt with are: (1) Regulatory functions of the capillaries; (2) regulation of the arterial bloodflow; (3) rôle of veins in regulation of the circulation; (4) rôle of the spleen in regulation of the circulation; (5) regulation of cardiac activity; (6) regulatory coördination of the organs concerned with the circulation.

H. B.

TUBERCULOSIS AMONG CHILDREN. By J. ARTHUR MYERS, PH.D., M.D., F.A.C.P. Pp. 208; 43 illustrations. Springfield, Ill.: Charles C. Thomas, 1930. Price, \$3.50.

THIS book deals with the epidemiologic and clinical aspects of tuberculosis in infancy, childhood and adolescence. The importance of contact with open tuberculosis, positive tuberculin reaction and roentgenologic examination in the diagnosis of pulmonary tuberculosis of the childhood type is emphasized as well as the relative unimportance of symptoms and physical signs. The author quotes liberally from current literature and summarizes our present knowledge of pulmonary tuberculosis in childhood. With the exception

of meningitis extrapulmonary tuberculosis is considered briefly. The usual difficulty is encountered that greatly reduced reproductions of roëntgenograms intended to show caseous or calcified lesions of the lymph nodes in most instances do not illustrate. This book will not be of great value to the advanced student of tuberculosis but should prove instructive to physicians and public health workers who, without adequate knowledge of the disease, deal with large numbers of children.

H. H.

MODERN OTOTOLOGY. By JOSEPH C. KEELER, M.D., F.A.C.S. Pp. 858; 105 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$10.00.

NOTHING new has occurred in otology in the past decade. On this account one is liable to view with tolerance the appearance of a new work on otology, as it so often is nothing more than another assembly of well-known facts written by someone who wishes to write a book. This work of the author, however, stands as a real contribution. The author has consulted a vast amount of literature, and the opinions on difficult subjects are not those of one, but of many observers. His chapters on embryology are especially good, and the presentation of clinical conditions is detailed and clear. A splendid bibliography is to be found at the end of each chapter. This book can certainly be recommended to the undergraduate, graduate student, general practitioner and specialist.

K. H.

HUMAN BIOLOGY AND RACIAL WELFARE. By Various Contributors. Edited by EDMUND V. COWDRY, PH.D. Pp. 612; 54 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$6.00.

THIS book should be of interest to physicians and biologists as well as educated laymen. Twenty-eight distinguished scientists have set forth in nontechnical language the present knowledge in the several subjects that comprise the study of man. The reader is made to realize that each science depends upon the other, and that it is largely because of the progress in such fundamental disciplines as physics and chemistry that rapid advances have been made in general biology and in the biologic aspects of man. The first part of the book deals with the extent of life in time and space. There is a discussion of such interesting questions as "Are there other inhabited worlds than ours?" "How long has life existed in this world?" "How long may it continue to exist?" The second part deals with the origin of man and contains chapters on evolution and the human race. In the third part of the book there is a

discussion of man as a physiologic unit. The present Reviewer would particularly invite attention to the chapter by Professor Cannon on "The Integrative Action of the Vascular System." The fourth part deals with the effects of environment. Among the papers of special interest to physicians are those by Sir Humphry Rolleston on "What Medicine has Done and is Doing for the Race," and by Professor Zinsser in "Adjustment to Infectious Diseases." In the final part the future of mankind is discussed; there are chapters on the inheritance of disease, on population growth, the mingling of races, and on the shaping of human opinion.

B. L.

BOOKS RECEIVED.

NEW BOOKS.

The Surgical Clinics of North America, Vol. 10, No. 3 (New York Number, June 1930). P. 265; 123 illustrations. Philadelphia: W. B. Saunders Company, 1930.

The Medical Clinics of North America, Vol. 13, No. 6 (Mayo Clinic Number, May, 1930). Pp. 275; 55 illustrations. Philadelphia: W. B. Saunders Company, 1930.

Progressive Medicine, Vol. II, June, 1930. Edited by HOBART AMORY HARE, M.D., LL.D. Pp. 416; 51 illustrations. Philadelphia: Lea & Febiger, Inc., 1930.

Guy's Hospital Reports, Vol. 80, No. 2, April, 1930. By various contributors. Edited by ARTHUR F. HURST, M.D. Pp. 252; 14 illustrations. London: The Lancet, Ltd., 1930. Price, 12s 6d.

Collected Papers of the Mayo Clinic, Vol. XXI, 1929. Edited by MRS. M. H. MELLISH, RICHARD M. HEWITT, B.A., M.A., M.D., and MILDRED A. FELKER, B.S. Pp. 1197; 279 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$13.00.

*Surgical Diagnosis, Vol. III.** By 42 American authors. Edited by EVARTS A. GRAHAM, A.B., M.D. Pp. 1044; 446 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$35.00, set of three.

*Alimentary Anaphylaxis.** By GUY LAROCHE, CHARLES RICHET FILS and FRANCOIS SAINT-GIRONS. Pp. 139. Berkeley: University of California, 1930. Price, \$2.00.

*Allergie des Lebensalters.** By DR. CLEMENS PIRQUET. Pp. 170; 142 illustrations. Leipzig: Georg Thieme, 1930. Price, M. 23.

Anatomische Organkrankheiten aus seelichen Ursachen. By LEOPOLD ALKAN, M.D. Pp. 142. Stuttgart: Hippokrates-Verlag, 1930.

The Basis of Epilepsy. By EDWARD A. TRACY, M.D. Pp. 92; 17 illustrations. Boston: Richard G. Badger, 1930. Price, \$2.00.

Infant Nutrition. By WILLIAMS MCKIM MARRIOTT, B.S., M.D. Pp. 375; 53 illustrations. St. Louis: The C. V. Mosby Company, 1930. Price, \$5.50.

* Reviews of titles followed by an asterisk will appear in a later number.

Some Social Aspects of Mental Hygiene. By FRANKWOOD E. WILLIAMS, M.D. Pp. 214. Philadelphia: The American Academy of Political and Social Science, 1930. Price, \$1.00 paper, \$1.25 cloth.

Reprints of 21 papers on various aspects of this important question.

Chemical Methods in Clinical Medicine. By G. A. HARRISON, B.A., M.D., B.Ch. (CANTAB.), M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 534; 65 illustrations. New York: The Macmillan Company, 1930. Price, \$5.25.

*An Introduction to Vertebrate Embryology.** By H. L. WIEMAN. Pp. 411; 150 illustrations. New York: McGraw-Hill Book Company, Inc., 1930. Price, \$4.00.

NEW EDITIONS.

Clinical Examination of the Nervous System. By G. H. MONRAD-KROHN, M.D., F.R.C.P. Pp. 222; 57 illustrations. Fifth edition. New York: Paul B. Hoeber, Inc., 1930. Price, \$2.50.

This deservedly popular volume contains as added matter: Two illustrations—Diagram of the Action of the Different External Eye Muscles and Lipiodol Shadow in the Cul-de-sac under Normal Conditions, a few additional notes on Trophic and Vasomotor States, together with the recent, important work pertaining to Ventriculography and Encephalography.

Ultra-violet Rays. By PERCY HALL, M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 248; 64 illustrations. Fourth edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$4.50.

Four editions in six years testify to the demand for this kind of book.

Physiology and Biochemistry in Modern Medicine. By J. J. R. MACLEOD, M.B., LL.D., D.Sc., F.R.S. Pp. 1074; 295 illustrations. Sixth edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$11.00.

"Steady increase in general knowledge, rather than discovery, has been the feature of the advances in physiology during the past three years, so that the changes in the present edition are spread throughout the volume." For reviews of previous editions of this work see this Journal 1927, 173, 723; 1923, 166, 136 and 1919, 158, 115.

Obstetrics for Nurses. By CHARLES B. REED, M.D., F.A.C.S., and CHARLOTTE L. GREGORY, R.N., B.S., M.D. Pp. 399; 144 illustrations. Third edition. St. Louis: C. V. Mosby Company, 1930. Price, \$3.00.

Minor Surgery. By ARTHUR E. HERTZLER, M.D., and VICTOR E. CHESKY, M.D. Pp. 602; 475 illustrations. Second edition. St. Louis: C. V. Mosby Company, 1930. Price, \$10.00.

The second edition of this book presents few changes from that of the first. Some 37 illustrations have been added and such additions to minor surgical procedures are given as a paragraph on injection treatment of varicose veins, and so forth. The book remains a very good and well illustrated minor surgery including, however, the technique of operations of many surgical procedures which could hardly fall into the minor surgical group.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND.

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Streptococci from Scarlet Fever, Erysipelas and Septic Sore Throat.—There has been a feeling among many bacteriologists, immunologists and even clinicians that the microorganisms responsible for scarlet fever, erysipelas and septic sore throat are very closely related, so closely, as a matter of fact, that it has been demonstrated more than once that the streptococci from septic sore throat and these other two diseases cannot be separated by toxin production and agglutination and that the toxins from streptococci from septic sore throat are rendered nontoxic by scarlet-fever antitoxin. TUNNICLIFF (*J. Am. Med. Assn.*, 1930, 94, 1213) has studied colonies of human streptococci on chocolate agar, a culture medium which contains defibrinated sheep's blood, Liebig's beef extract and agar. Using this particular medium in the study of the streptococci of the three diseases mentioned above, she finds that on the chocolate agar the color reaction differs, when streptococci are isolated from cases of scarlet fever, from those isolated from patients suffering from erysipelas. She believes that this is further evidence of their etiologic difference. The author mentions, also, that she has examined by the opsonic method strains of streptococci isolated during epidemics of sore throat. It is found that they belong neither to the scarlet fever or the erysipelas group. The strains from septic sore throat were capable of producing a bright green color on chocolate agar and the cultures from the two types of streptococci produced colonies which are quite distinct. One is warranted in feeling that as a result of these studies there is an etiologic difference between the three groups of streptococci. The reader would be definitely convinced were there not other observations so totally divergent in their results.

Relation of Diet to the Production of Dental Caries in Young Rats.—

One of the statements frequently made by dentists is that dental caries occurs in children as a result of vitamin deficiencies. Furthermore, the statement is often made that it may be produced likewise by a deficiency of mineral salts. KNOWLTON (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 757) selected a variety of diets which were fed to rats from an inbred colony. Thirty-seven rats were kept on these varied diets, usually for an average of about forty-five days. The biologic incompleteness of the diet is indicated by the marked reduction in growth of the test animals as contrasted with the controls. There was a significant difference also in the calcium and phosphorus content of the teeth of the rats which were on one of the test diets. The young rats in no case developed dental caries. "The tests indicate," says the author, "that in the young rat dental caries probably does not result from the use of diets low in vitamin A, B or D or by a deficiency of mineral salts."

Neutralization of the Virus of Poliomyelitis by Human Sera.—

SHAUGHNESSY, HARMON and GORDON (*Proc. Soc. Exper. Biol. and Med.* 1930, 27, 742) review somewhat briefly the literature on the neutralization of the virus of poliomyelitis by the sera of individuals recovered from an attack of the disease. The reactions, however, have never been studied in a quantitative manner. In the present experiments, Berkefeld filtrates of 5 per cent emulsion of spinal cord containing the virus were mixed in 1.5 cc. quantities with an equal quantity of the serum dilution studied, incubated at 37° C. for two hours and 2 cc. injected into the brain of the monkey. Their results are presented in tabular form; suffice it here to say that the sera of contacts, of normal adults and of children have an equal power at least, and probably more power, to neutralize the virus than the sera of people who have had the disease. The sera of infants seem to be almost lacking in effect upon the virus. The important feature of the study, of course, is that normal sera may be used in the therapeutics of poliomyelitis.

Effect of Bile Salts on the Blood Calcium.—In jaundice it has been known for some time that there is disturbance of calcium metabolism and recently the disorder has been treated in a certain number of instances by the intravenous injection of calcium chlorid. This has usually been the method employed in order to increase blood coagulation time preparatory to surgical operation, but at the same time it has been noted that there has been a considerable improvement in the symptom of jaundice. The blood calcium has been shown to be extremely low in this condition. EMUND ANDREWS, REWBRIDGE and HRDINA (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 755) undertook to investigate certain phases of disturbed calcium metabolism in jaundice. They injected a 10 per cent solution of bile salts intraperitoneally into dogs and administered it likewise to another group intravenously and very promptly there occurred marked lowering of this blood calcium. Following a short preliminary rise there was this marked fall. The authors are not prepared to give an explanation of this phenomenon, but point out that the obvious fact of the insolubility of the calcium compounds of bile acids suggests their precipitation.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Papillomas of Choroid Plexus.—VAN WAGENEN (*Arch. Surg.*, 1930, 20, 199) says that two cases of papilloma of the choroid plexus are reported. In one the tumor was surgically removed from the left lateral ventricle, with relief of symptoms. The second case represents the observation at necropsy of a huge papilloma of the choroid plexus with true "seeding" of the tumor *via* the cerebrospinal fluid. The reports of about 45 cases have been collected from the literature which, so far as one can determine from the descriptions given, seem to have arisen from the choroid plexus. A few of these presented the phenomenon of seeding. The favorite site for these tumors is in the fourth ventricle. The age incidence was greatest in first decade and gradually diminished up to the sixth decade. The surgical removal of this type of tumor is feasible, especially with the aid of electrosurgical devices. Preliminary Roentgen treatment in the author's cases appeared to have reduced the vascularity greatly. A considerable part of the non-obstructive hydrocephalus found with tumors of the choroid plexus may well be associated with the increased epithelial surface.

Chronic Recurring Temporomaxillary Subluxation.—MORRIS (*Surg., Gynec. and Obst.*, 1930, 50, 483) writes that temporomaxillary subluxation is a definitely distinct entity, the pathologic condition of which is characterized by a distortion of the normal relations of the joint meniscus leading to capsular relaxation. Resulting disturbances in joint mechanics are responsible for a variety of joint dysfunction best known as snapping jaw. Commonly seen as a painless, noisily functioning joint the efficiency of which is not at all impaired, it is occasionally encountered in the form of chronically recurring attacks of pain and locking, requiring immediate treatment. There exists an unexplained reluctance to apply to this joint the radical operative measures, which have become the accepted treatment for analogous minor lesions of other joints. Failure to take into consideration the pathologic physiology of temporomaxillary subluxation has been responsible for a large number of proposed methods of treatment representing a wide divergence of principles. Two methods of treatment are emphasized which are based upon sound surgical principles and upon a study of the mechanics of the joint. Utilization of these methods should standardize treatment and demonstrate the practicability of accepting a larger group of these cases for radical operation.

The Indwelling Ureteral Catheters in Urinary Surgery.—GUTIERREZ (*Surg., Gynec. and Obst.*, 1930, 50, 441) states that the indwelling ureteral catheter is of value in urinary surgery, not only in regard to diagnosis and treatment but as a convenience during and after opera-

tion. It is essential that the catheter must serve its purpose, that is, secure drainage, relieve pain and correct infection. When double drainage is required the special urethral catheter should be easily passed, it being inserted through the inlying ureteral catheter. The most striking results are obtained with this method of treatment in "renal colic," ureteral calculi, pyelitis and pyelonephritis, the so-called idiopathic hematuria, urinary stasis with or without infection and in calculous anuria. Also in certain instances when elimination of urine is insufficient, forced fluid and daily intravenous infusion are highly desirable. After operation it will serve to secure drainage and prompt healing of the wound without leakage of urine or the formation of permanent fistula. Also after operation it will serve too to divert the urine from the bladder, particularly in operations on vesicovaginal fistulae, thus permitting the bladder to heal without infection from urine. The technique of the indwelling ureteral catheter is merely that of cystoscopy and catheterization of the ureters.

Phrenic Exaeresis in the Treatment of Pulmonary Tuberculosis.—FRANK and MILLER (*Ann. Surg.*, 1930, 91, 669) believe that phrenicectomy is a valuable aid in the treatment of pulmonary tuberculosis in selected cases. Of 100 patients so treated, 90 per cent of whom were far advanced, 40 per cent showed improvement. In 8 the sputum became negative for tubercle bacilli and in 8 the cavities disappeared. Phrenicectomy is an adjuvant in artificial pneumothorax, and should be considered in every case with cavitation. Following avulsion of the phrenic nerve 44 per cent of the cases showed a better collapse. A good phrenicectomy is better than a poor pneumothorax. It is less hazardous, less discomforting, unattended with complications and is a necessary preliminary to thoracoplasty. The good results of phrenicectomy are not dependent on the location of the pathology, but rather on the retractibility of the pulmonary tissue. Basal and midlobe lesions offer most and cavities above the clavicle least, although in the latter with a marked elevation of the diaphragm good results are obtained.

Treatment of Bronchiectasis: Multiple Stage Lobectomy.—CORYLLOS (*Arch. Surg.*, 1930, 20, 767) says that a clinical classification distinguishing different forms of bronchiectasis is suggested, and the practical usefulness of these distinctions has been set forth. The necessity for using a prolonged and progressive treatment against a chronic and progressive disease is shown. In advanced forms of bronchiectasis only eradication of the diseased parenchyma of the lung can produce a cure. This, according to the case, should be done by resection (lobectomy), cauterization, cautery pneumectomy of Graham or exteriorization (Whittemore). In order to decrease the mortality incident to these operative procedures, a technique of multiple stage lobectomy is outlined in which the following stages are systematically performed in the order named: Artificial pneumothorax, phrenicectomy, thoracoplasty and lobectomy. In support of this method, physiologic, pathologic and clinical data have been presented. Two cases of advanced bronchiectasis, in which cure was achieved by the use of this technique, are reported.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

Comparative Studies of a Heart Hormone Preparation and Extract of Voluntary Muscle.—FAHRENKAMP and SCHNEIDER (*Med. Klin.*, 1930, 26, 48) report the results of comparative studies on man of an extract of heart muscle previously believed by Haberlandt to represent a cardiac hormone and an extract of voluntary muscle prepared so as to be free from albumin, histamin and epinephrin. They find that the extract of voluntary muscle produces identically the same effects as does that obtained from the heart muscle and they therefore conclude that there is no evidence in favor of the latter representing a true heart hormone. The actions manifested by these two extracts are marked slowing of the ventricular rate, both in fibrillating patients and in those with sinus rhythm when the extract is administered to patients orally under the influence of digitalis. Both extracts administered either orally or intravenously to patients with recurring seizures of angina pectoris control the attacks almost completely. However, if administered to patients under the influence of digitalis, the extracts may produce symptoms of angina pectoris. In patients with continued very high blood-pressure and sleeplessness the continued use of these extracts improves the patient's subjective symptoms and usually leads to a return of the ability to sleep. For oral use a dose of from 15 to 60 drops per day usually suffices. In severe cases of angina, more immediate action is obtained by an intravenous dose of from 1 to 2 cc. At present the dosage must be regarded as experimental. Intravenous administration of a dose of 1 cc. produces a transitory sense of warmth in the head accompanied by redness of the face, both of which phenomena disappear within two or three minutes. Occasionally the patient complains of a pulsating, painful sensation in the upper abdomen. This also is harmless and passes rapidly. Patients with high blood pressure usually show a fall of from 10 to 30 mm. of mercury, while those without high blood pressure frequently show a transitory rise of about the same amount.

The Action of Some of the Newer Drugs on the Circulation.—Finding that there is an inadequacy of trustworthy information with reference to the actions of a number of the newer remedies in states of circulatory insufficiency, TRENDLENBURG (*Med. Klin.*, 1929, 25, 1573) reports the results of a careful analysis of several of these drugs on the basis of his own pharmacologic experiments. He concludes that, for the relief

of true cardiac insufficiency, digitalis and strophanthus are unrivaled. They have the great advantage over all other drugs advocated for use under these circumstances of improving the work of the heart without exercising any significant constrictor effect upon the peripheral blood-vessels and, therefore, without increasing the peripheral load against which the heart must work. Both epinephrin and ephedrin stimulate the heart powerfully but simultaneously constrict the peripheral arteries so that their stimulant effects upon the heart are largely overcome by the increased peripheral resistance. Cardiazol, coramin and hexeton have exceedingly little or even no action upon the circulation which will overcome cardiac failure and hence are practically useless in that condition. They, however, do produce a transitory stimulation of the depressed respiratory center and may be of slight benefit thereby in diminishing the lack of oxygenation of the blood and in increasing elimination of carbon dioxide. In the very rare condition of true vascular insufficiency epinephrin and ephedrin are far the most useful drugs. Digitalis and strophanthus are of no value and cardiazol, coramin and hexeton are too feeble in their effects upon the vasomotor mechanism to be trustworthy. Where there is a combination of cardiac insufficiency with vascular insufficiency, epinephrin and ephedrin again are the drugs of first choice while the other two discussed here are of relatively little value. They must be employed however with great care in order to avoid overconstriction of the bloodvessels and thereby do greater harm than good. Cardiazol, coramin and hexeton may sometimes be somewhat helpful in combination with either digitalis or epinephrin where there is a considerable degree of respiratory depression, but alone none of these agents is capable of overcoming either of the two forms of circulatory deficiency.

Investigations on the Peroral Insulin of Stephan (Cholosulin).—STEPHAN (*Deutsch. med. Wchnschr.*, 1930, 56, 88) reports further studies on the action of his peroral form of insulin. This preparation is an addition compound of insulin with the sodium salt of desoxycholic acid. He contends that, when properly administered, that is when given to the patient during fasting, this preparation permits the absorption of insulin through the portal vein. Only a portion, however, of the insulin so administered and absorbed exerts an immediate action, the remainder according to his contention being fixed in the liver and giving rise to a prolonged and evenly-sustained insulin action. Investigations confined to a period of a few hours, therefore, seem to show that this preparation is much less active in the control of diabetes than is the usual preparation of insulin administered subcutaneously. In order to test the theory that this partial fixation of insulin is due to absorption through the portal vein, Stephan reports investigations embracing the use of his preparation by subcutaneous injection both in normal individuals and in diabetic persons. From these investigations he finds a similar mild early insulin action both on blood sugar and on glycosuria and a prolonged late action due to temporary fixation. He concludes that the combination of insulin with desoxycholic acid is responsible for this altered action. He also contends that the use of

cholosulin is never accompanied with the danger of insulin shock in either normal or diabetic persons and that even with very large doses its optimal action is not exceeded owing to fixation of a large portion of the dose. The preparation thus differs essentially from ordinary insulin, bringing about a mild initial action which is followed by a well-sustained control of blood sugar. However, Stephan does not believe that the preparation is inferior to ordinary insulin in the control of diabetes, whether it be given by mouth or by subcutaneous injection.

UMBER and ROSENBERG (*Deutsch. med. Wchnschr.*, 1930, 56, 169, 213) subjected Stephan's cholosulin to a very accurately controlled investigation in a small group of cases, administering it exactly as recommended by Stephan both by mouth and by subcutaneous injection. They find that only with exceedingly large doses, 100 to 500 units, is there even a mild diminution of glycosuria. In the most favorable instances in man, only 5 per cent of the insulin so administered by mouth becomes active in the burning of sugar. The antiglycosuric action of cholosulin is so small and so uncertain that the preparation cannot be considered of value in the treatment of diabetes when administered by mouth. The authors are able to find no qualitative differences between the action of cholosulin and ordinary insulin and are unable to discover any evidences of its temporary storage and subsequent release in the body. The action of cholosulin administered by mouth is so uncertain and so insignificant that the authors find no definite evidences of its capacity to diminish alimentary glycosuria. They find essentially the same deficiencies when this preparation is administered subcutaneously, although under these circumstances there is a slightly delayed reduction in the blood sugar appearing from six to nine hours after injection. However, in controlled experiments, a delayed fall in blood sugar of equal magnitude is observed after the injection of 1 gm. of desoxycholic acid and an equal fall occurs even in well-controlled cases to whom no medication is administered. From their investigation the authors conclude that there is no evidence that Stephan's cholosulin is of any practical value in the treatment of diabetes.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Underweight Children—Increased Growth Secured Through the Use of Wheat Germ.—MORGAN and BARRY (*Am. J. Dis. Child.*, 1930, 39, 935) compared two groups including from 31 to 47 underweight children between the ages of eleven and thirteen years as to growth in weight, height and certain other physical measurements over three periods

totaling thirty weeks. Each child in one of these groups in each period was required to include in the noon meal 3 ounces of rolls made with 50 per cent wheat germ and 50 per cent white flour. A control group took the usual white flour rolls. The test group took a total of 5 ounces of wheat germ per week. It was noted that the weight increases in each of the wheat germ periods were about three times as great as in the control periods. The difference in all cases was five or more times greater than the probable error of the difference. The height increases were significantly greater in two of the wheat germ periods than the two of the corresponding control groups. Alveolar carbon dioxide tension was increased in a greater percentage of the wheat germ-fed children than in the controls and it is thought that this change was due to the diminished acidosis following increased food intake. The significance of these observations is based on the recent discovery of the multiple nature of vitamin B and of the poverty of the major foods such as fruits, vegetables, milk and meat in the antiscorbutic substances. The authors point out the importance of whole cereals but most particularly of grain embryo such as those of wheat and rice as a possible source of this vitamin. They also point out probable relationship of the decreasing vitamin B content of the modern diet to decreased appetite in children, nervousness, constipation and possibly other gastrointestinal disturbances.

Chronic Subdural Hematoma in Infants.—SHERWOOD (*Am. J. Dis. Child.*, 1930, 39, 980) presents 9 cases in which he describes a definite clinical syndrome. The pathologic changes in the disease called pachymeningitis interna hemorrhagica may vary considerably due to the fact that in the past many conditions involving the dura have been described as pachymeningitis. The term chronic subdural hematoma describes the condition found in the 9 cases presented in his report. The etiology is obscure and it was unusual to find that in 5 of the 9 cases the patients were cared for in institutions or by foster-mothers. Trauma due to injury at birth or other means is a possible factor although in these particular cases it was not proved. Infection is important only as a complication. Syphilis is also a possible cause as is also a bleeding diathesis but the latter could not be proved in any of these cases. This condition should be thought of in every case in which there are convulsions and enlargement of the head and should be confirmed by a subdural tap. This operation should be done with a hypodermic needle with a small syringe in order to avoid trauma to cerebral veins in case no chronic subdural hematoma is present. After the diagnosis is established a small lumbar puncture needle can be used to drain the cyst under the strictest asepsis as these hematomas easily become infected. After the active process has subsided the patient should have the benefit of a neurosurgical consultation in order that more definite treatment can be used, if necessary. The prognosis as a whole is good in the absence of intercurrent infection, but everything should be done to raise the patient's general resistance in order to prevent such an occurrence. Many cases are followed by a sequela.

The Use of Gelatin as a Supplementary Food in the Infant's Dietary.—ELTERICH, BOYD AND NEFF (*Arch. Pediat.*, 1930, 47, 286) studied 11 cases of whom 7 were males and 4 were females. Of this group there were 5 colored and 6 whites of whom one was Italian and one was Russian. These infants were studied on 1313 experimental days of which 719 were gelatin days and 594 were not gelatin days. There was a gain per twenty-four hours on gelatin of 0.85 ounces. There was gained per twenty-four hours not on gelatin 0.98 ounces. The average gain per twenty-four hours was 0.91 ounces. These results show that babies average about 1 ounce less in gain per week when on gelatin although the same number of calories were used. These results are according to expectations for when gelatin was given the formula contained a very high protein content, while when gelatin was not used the formula contained an average of protein and carbohydrate. It is a well-known fact that babies frequently gain rapidly on the excessively high-carbohydrate diet as is seen in babies fed on condensed milk, for this reason the increase in weight should not be the only standard used in the estimation of the healthy growth of infants. Such points as tissue turgor and hard, well-developed muscles are important considerations. It was noted by the observers that many factors which have been discussed by others such as tracheal coughs, running nose, and other parental infections almost invariably influenced the gain in weight. In spite of the relative large amount of protein in these gelatin formulæ no evidence of the so-called protein fever was observed. This absence of protein fever may have been due to the ample supply of liquid in the diet, a fact that was originally pointed out by Finkelstein. During certain periods of the observation, three times the quantity of protein matter was given to the infants that is given in the average every-day formulæ. This high-protein feeding was maintained for stretches of more than three weeks without any apparent untoward results.

Nephritis in Childhood.—ALDRICH (*J. Am. Med. Assn.*, 1930, 94, 1637) has been accustomed not to limit the fluids in any case of nephritis regardless of the amount of edema present. He follows this method of treatment because he felt that patients were toxic and that withholding of liquids could not be sound therapeutics in some patients. He suggests that edema may be a protective mechanism designed to dilute toxins. He feels that this method of treatment is justified by the observations that he has made that patients are much less toxic and more comfortable during the administration of sufficient fluids and he does not fear edema except in those cases where it involves the brain, lungs or larynx. On the other hand he has found that definite restriction of liquids has been responsible for accidents which have occurred in his experience. As a result of his feeling toward fluid he has evolved a technique for the treatment of convulsive anemia which has been used with great success in the elimination of accidents from this cause.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Arsenic Findings in Eczema and Allied Conditions in Infants and Young Children.—VAN DYCK, THRONE and MYERS (*Arch. Pediat.*, 1930, 47, 218) carried on the previous work of Throne and Myers in a study of the possibility of arsenic as an etiologic factor in eczemas. Urine specimens from 105 infants and young children with eczema or urticaria were examined for arsenic, using Myers' modification of the Marsh test. In 50 cases (48 per cent) no arsenic was found; the remaining 55 cases showed the presence of arsenic ranging from 0.04 to 2.3 mg. per 100 gm. of the dried specimen. Eleven control patients with one exception gave negative results. The single instance was the discovery of 0.12 mg. of arsenic in a young child who had previously received thallium acetate for tinea capitis. The controls represented such conditions as impetigo, scabies, acute dermatitis and pediculosis. Breast-milk specimens from mothers who were nursing babies with eczema contained arsenic in 40 out of 55 cases examined (72 per cent). The amounts ranged from 0.012 to 3.5 mg. per 100 gm. of solids. Fifteen normal controls were negative for arsenic except 2 specimens which contained 0.06 and 0.09 mg. The sources of arsenic are widespread and are found in all sorts of foods, including fruit, vegetables, fish, milk and candy. Sodium thiosulphate in salol-coated tablets, of $2\frac{1}{2}$ grains each, and given three times a day before meals, seemed to be almost specific in cases where large amounts of arsenic were found. For infants the tablets were crushed and the powder given with the milk or cereal. In some cases where no arsenic was found the sodium thiosulphate seemed to give temporary relief. The authors' work, in their opinion, justifies the previous conclusions of Throne and Myers, that arsenic is an important factor in about 30 per cent of cases diagnosed clinically as eczema.

A List of Cutaneous Irritants.—Under this title WEBER (*Arch. Dermat. and Syph.*, 1930, 21, 761) has listed a complete outline of all known and reported cutaneous irritants that have been productive of dermatitis and eczema. The irritants are classified under Hair Dyes and Hair Tonics, Cosmetics, Irritating Plants of the United States, Tropical Plants and Unclassified Irritants in Alphabetical order. The inclusion of a comprehensive bibliography makes this a most usable contribution. The American Medical Association is publishing this report as part of its series of pamphlets for ready reference.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Surgical Treatment of Cancer of the Cervix.—Due to the fact that radium is so extensively used in this country in the treatment of cancer of the cervix, it has been necessary for some years to turn to European clinics in order to determine the present status of the radical operation. BONNEY (*Lancet*, 1930, 218, 277), who is one of the foremost English gynecologists, states that he has performed 382 Wertheim operations, of which 284 were done over five years ago and, therefore, are of value in determining the end results. His analysis of this series is as follows:

Immediate mortality	47 (16.5 per cent)
Recurrence within five years	107
Untraced	12
Died of intercurrent disease	8
Well at the end of five years	110
	<hr/>
	284

He is convinced that the mortality of the operation decreases with increasing experience of the operator, and as evidence presents the following table:

	Operations.	Deaths.	Mortality, per cent.
1907 to 1910	110	22	20.0
1916 to 1924	174	25	14.3
1925 to 1929	98	8	8.1

The factors which have been of value in the reduction of the mortality include spinal anesthesia in combination with full ether anesthesia in order to combat shock; packing the vagina tightly with gauze soaked in violet green to combat infection; protection of the abdominal wound with two layers of rubber dam and the use of automatic retraction; separation of the bladder and rectum from the vagina by the sense of touch; exposure of the uterine arteries before ligation close to the internal iliac arteries; complete isolation of the lower 2 inches of the ureters; division of the cardinal ligaments by the sense of touch; extensive removal of the vagina, the lower end which remains being left open and the extirpation cavity in the pelvis packed so that the packing comes out at the vulva; and finally, the routine removal of the regional glands. While he has performed the operation in as short a time as twenty-seven minutes, he has found that his average time is about one

and a quarter hours. Immediately after operation he gives intravenous saline solution or blood transfusion in order to anticipate shock. He does not see any advantage in using radiation as an adjunct to operation either pre- or postoperatively. Of the 284 cases in this series, the regional glands removed were cancerous in 124 and not cancerous in 160, so that the gland involvement rate was 43 per cent. The five-year survival rate for the gland-free group was 49.9 per cent as compared with 23.3 per cent for the gland-involved group. Of his private cases, on which he has very careful records, his operability rate in 106 cases seen was 78 per cent, with relative cure in 48 per cent and absolute cure in 37.5 per cent. Of this group there was gland involvement in 40 per cent of the cases operated upon. In view of such excellent results, naturally he is very enthusiastic about operation, believing that the best results in the treatment of cancer of the cervix are to be obtained by operation by skilled surgeons in all operable cases, while the remainder should be treated with radium. We are not at all surprised at Bonney's views on this subject when backed by statistics which are so good, but there are few clinics, let alone individual surgeons, where such results can be equalled or even approximated, and it is for this reason that the large majority of gynecologists have abandoned the radical operation in favor of irradiation.

Treatment of Complicated Dermoid Cysts.—In describing some of the complications to which ovarian dermoid cysts are subject and the appropriate treatment, COUNSELLER (*Surg. Clin. North America*, February, 1930, p. 151) states that the diagnosis of dermoid cyst is rarely made before operation, as they are comparatively slowly growing tumors. They often become fixed in the pelvis by attachment to the rectum or vagina and then become secondarily infected. When supuration occurs perforation into the rectum, vagina or bladder usually takes place, and the resultant fistula is apt to remain for months or years unless the content of the cyst is completely evacuated. In such cases it is far safer to dilate the fistulous tract, evacuate the cyst as thoroughly as possible and scrape the inner wall with a sharp curette so as to eradicate the epithelial lining and all dermoid structures. If the wall of the cyst has not been punctured by the curette the cavity should be irrigated thoroughly with warm salt solution and packed solidly with iodoform gauze. The gauze is gradually removed and the cyst and fistulous tract will contract down to a scar. He cautions that it is extremely difficult and dangerous to remove a dermoid cyst which has perforated externally by the abdominal route on account of the high risk of general peritonitis, the deep situation of the tumor in the pelvis and the dense adhesions of the wall of the cyst to adjacent structures. In cases in which torsion of the pedicle of a cyst has been diagnosed, abdominal exploration should be immediately performed. As a rule, in such cases the blood supply is practically shut off and if the cyst is a dermoid it may perforate into the peritoneal cavity and produce fatal peritonitis.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Permanent Relief of Pain in Absolute Glaucoma and Ciliary Neuralgia by Anesthetization of the Gasserian Ganglion.—Two problems are still unsolved in the treatment of pain in ophthalmology: permanent relief of pain in the blind eye, which should be retained for cosmetic reasons, and the permanent relief of pain in the functioning eye. Resection of the ciliary ganglion frequently leads to permanent paralysis of ocular muscles, to perforation of the sclera necessitating later enucleation. Orbital injection of alcohol also may be followed by paralysis of the ocular muscles and its success and permanence is uncertain. To avoid all these undesirable sequelæ ALEXANDER (*Klin. Monatsbl. f. Augenh.*, 1930, 84, 65) recommends alcohol injection of the Gasserian ganglion such as is done in trigeminal neuralgia. He reports 2 successful cases: in the first there was pain in the right eye and entire side of the head due to secondary glaucoma following thrombosis of the central retinal vein. Continuous vomiting accompanied the pain. Alcohol injection resulted in permanent anesthetization of the first and second branches and absence of corneal reflexes. Full sensibility was retained in the third branch. The vomiting ceased as soon as the pain was relieved. There has been permanent relief for two years. In the second case uncontrollable pain was present in the first branch, particularly in the eye which was functioning. The first injection of alcohol gave relief for a year; the second injection was given as soon as there was a slight recurrence. The permanent relief has lasted more than five years. There is full visual acuity and a smooth cornea; the corneal reflex is absent. Alexander considers that alcohol injection of the Gasserian ganglion is the only method which will give permanent relief without cosmetic deformity in uncontrollable pain in the blind and particularly in the functioning eye.

Alcohol Injections in the Treatment of Blepharospasm and of Spastic Entropion.—Essential blepharospasm is much more difficult to treat than symptomatic blepharospasm in which the basic disease may be attacked and the spasm relieved. Alcohol injections to produce akinesia of the facialis without paralyzing it has been used by SAFAR (*Ztschr. f. Augenh.*, 1930, 71, 135) and others with success. The author injected about 2 to 3 cc. of 4 per cent solution of novocain followed by 2 to 3 cc. of 80 per cent alcohol to obtain the greatest possible blocking of the afferent fibers of the facialis. The novocain mitigates the burning sensation caused by the alcohol. The injection is made uniformly, corresponding to the temporal circumference of the orbital border outside the orbital border; the depot is placed into the muscle, not subcutaneously. The action of the injection is immediate. The author reports 2 cases of blepharospasm in which he has used this akinesia

and 2 in which he has used it in spastic entropion. In these 2 instances he used only "half akinesia"—1 to $1\frac{1}{2}$ cc. alcohol. He recommends the treatment because it is slight and ambulatory and warrants further use.

Metastatic Bacillus Coli Panophthalmitis from Calculus Pyonephrosis.—While metastatic panophthalmitis is not uncommon, *Bacillus coli* infection in such cases is rare and no case of proven infection from the kidneys has been reported. Experimental work has shown that bacteria can pass from the blood stream into the vitreous of normal, unirritated eyes. Injured eyes are more favorable for their entrance. There are three types of inflammation: An intense one, with symptoms of panophthalmitis and possible rupture; iridocyclitis, with hypopyon, vitreous complications and eventual atrophy; an insidious, slightly inflammatory condition which gradually becomes apparent and in children simulated glioma. LEVINE (*Arch. Ophthalmol.*, 1930, 3, 410) reports the case of a man, aged thirty-eight years, in whom the metastatic infection could be traced to the kidneys. The patient came complaining of redness and pain in the eye. Two days previous he had had a left-sided renal colic; he had had similar attacks for six years. The right kidney had been removed seven years ago for calculus pyonephrosis. The inflammation of the eye increased, so that two days later an incision was made to allow the escape of pus which was cultured and then evisceration was performed. The culture proved to be a pure growth of *Bacillus coli*. A similar pure growth was obtained from a catheterized specimen.

Argyll-Robertson Pupils in Polyneuritis: Report of a Case and Theoretical Deductions.—In all, NIELSEN and VERITY (*Ann. Int. Med.*, 1930, 3, 707) have listed fifteen causes of Argyll-Robertson pupil: Syphilitic processes; disseminated sclerosis; polioencephalitis; diabetes mellitus; sulphid poisoning; congenital; syringobulbia; diffuse toxic-infective states; finally, a case in which no cause could be found, but which progressed through the Argyll-Robertson to complete ophthalmoplegia interna, but with development of pupillary contraction whenever the patient swallowed anything. The authors now present another case in which Argyll-Robertson pupil appeared in polyneuritis; it seemed to them to bear out Ingvar's theory as to the pathology of reflex immobility. Ingvar considers that only such processes as manifest themselves in producing marginal destructions within the basal subarachnoid spaces of the brain are able to cause the Argyll-Robertson pupil. The patient, a man, aged sixty-two years, was admitted to the hospital with acute polyneuritis apparently of a toxic and not syphilitic nature. Argyll-Robertson pupil was found which had completely disappeared at the end of nine days. With the regression of the polyneuritis the optic neuritis also diminished. Evidence of central neuritis could not be shown above the level of the D8 segment; bilateral optic neuritis and considerably increased globulin in the spinal fluid was found. There was, therefore, inflammation of the regions traversed by the afferent pupilomotor fibers. With the onset of this inflammation Argyll-Robertson pupil appeared and with its regression disappeared. The authors, therefore, consider that this case corroborates Ingvar's explanation of the pathogenesis of reflex immobility of the pupils.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

Osteogenesis of the Human Periotic Capsule.—The petrous portion of the temporal bone and especially the otic capsule is of interest from a purely embryologic and anatomic standpoint because of its unique structure. In the realization that a thorough knowledge of the development and structure of this bone may prove of importance in solving the mystery surrounding otosclerosis and its supposed relation to that dreaded disease—progressive deafness, BAST (*Arch. Otolaryngol.*, 1929, 10, 459) calls attention to the fact that the texture of the bone in the otic capsule differs from that of the other bones and that the outstanding difference is the normal presence of so-called calcified cartilage. Inasmuch as the significance of this incomplete replacement of cartilage by bone in this particular bone and not in other bones is still unknown, the author, in full recognition of the importance for a better understanding of this structure, sets forth a detailed account of his observations concerning the osteogenesis of the bony otic capsule. Following a masterful presentation, supplemented by microphotographs, Bast concisely summarizes his findings. This recapitulation includes such pertinent anatomic data as : (1) the bone of the periotic capsule is of three types—perichondral, endochondral, and intrachondral; (2) an exposition by the process by which the ossification of the cartilaginous capsule begins; (3) a description of an area known as fissula ante fenestram (Siebenmann) or Cozzolino's zone (Perozzi), and (4) of another structure known as canalis membranceus cæcus (Ibsen) or as fossula post fenestram (Siebenmann).

Otosclerosis in Its Histogenic Relations to Osteodystrophia Fibrosa (Ostitis Fibrosa).—Having established a foundation for further studies of bone pathology—especially osteodystrophia fibrosa and otosclerosis—in a previous communication,¹ and inasmuch as no special critical comparison of these two diseases from the standpoint of histogenesis has appeared considering the most recent contributions to the pathology of osteodystrophia fibrosa, WEBER (*Arch. Otolaryngol.*, 1930, 11, 1) reports a very comprehensive study in this connection. In contradistinction to earlier authors, the question of otosclerosis is approached from studies made on osteodystrophia fibrosa, which is kept in the limelight. Weber regards the present contribution as supplementary to his recent publication having to do with the nature of osteodystrophia fibrosa (*Beitr. z. allg. Pathol. u. path. Anat.*, 1929, 82, 383). Briefly, Weber has concluded from his observations that both otosclerosis and osteodystrophia fibrosa represent a degenerative, reactive, reparative process. The typical focal otosclerosis is histogenetically identical

¹ Vide retrospect: *AM. J. MED. SCI.*, 1929, 178, 292.

with a local osteodystrophia fibrosa and may be regarded as a local hyperostotic porotic or local hyperostotic sclerotic form of osteodystrophia fibrosa, an "osteodystrophia otosclerotica." It belongs to the metapoeitic diseases. Only the cases representing such focal involvement of the labyrinthine capsule ought to be designated as otosclerosis (genuine otosclerosis). In cases of generalized osteodystrophia fibrosa the diagnosis "otosclerosis" is possible, from the histopathologic standpoint, only in von Recklinghausen's disease (ostitis fibrosa) and then only in case the changes are superimposed and themselves represent as hamartoplasia the pseudotumor. The localization of the genuine otosclerosis in the majority of these cases leads to deafness due to stapedia ankylosis (so-called clinical otosclerosis). It is possible, however, that some of these cases with typical histopathologic otosclerosis do not reveal the clinical aspect of otosclerosis, namely, ankylosis of the stapes. Contrariwise, it is possible that certain cases with no histopathologic otosclerosis may reveal the clinical aspect of otosclerosis owing to stapedia ankylosis. These cases must be regarded not as otosclerosis, but rather as a purely generalized osteodystrophia fibrosa.

A Contribution to the Etiology of Progressive Deafness. Preliminary Report.—In a study of the acinous and insular function of the pancreas in 9 cases of otosclerosis and 12 cases of nerve deafness, GOTTLEB (*Laryngoscope*, 1930, 40, 85) found definite lowering of the digestive capacity in one or more of the pancreatic ferments in fourteen instances, and blood sugar levels higher than the average normal in five. Although the majority of cases treated with pancreatic extract showed improvement, the author is skeptical as to the conclusive value of this therapy in progressive deafness, especially in otosclerosis. Of the 4 patients with nerve deafness who were given pancreatic extract, all improved. The audition in 4 of the 5 persons yielding high blood-sugar values or glycosuria became more acute after treatment.

Studies in Action Currents in Laryngeal Nerves.—In order to ascertain more about the neurophysiologic mechanism of phonation, LINDEMANN (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 479) recorded action currents from the inferior and superior laryngeal nerves during voice production in dogs, using a 3-element Westinghouse oscillograph. It was found that when no voice was produced the action current line was practically at rest, whereas during voice production the action current line of the inferior laryngeal nerve showed regular oscillations having the same frequency as the voice line and changing with the pitch of the voice. Additional experiments led the author to assume that potential changes travel from the central organ to the larynx, although he does not feel justified in considering these regular action-potentials as originating in the higher centers of coordination. Records taken from the superior laryngeal nerve indicated that this nerve is largely sensory. Believing that a proprioceptive mechanism is responsible for the regular oscillation observed in the laryngeal nerve, the author states that further research will be necessary to study the suggested proprioceptive control of the action of the vocal cords.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

The Abscess of Pott's Disease.—GHORMLEY (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 510) notes that the thoracic abscess of Pott's disease as seen with the Roentgen ray is of three types—the fusiform, the pyramidal and the globular. From a prognostic standpoint the globular type foretells a better course than the others. The pyramidal and fusiform varieties represent more extensive dissection beyond the original focus. Calcification of the contents of these abscesses occurs frequent and may appear as flocculent or flaky areas in the shadow or the entire shadow becomes dense; the calcification is of favorable significance, but cannot be regarded as an indication of complete healing. It is well known that fewer vertebræ are involved by about one-half in the average case of lumbar Pott's disease as compared with the thoracic variety. Any enlargement of the normal psoas shadow or along it, accompanying a spinal lesion, is presumptive evidence of tuberculosis of the spine with psoas abscess. Subsequently the abscess may absorb and leave little or no evidence of its former existence. Or it may calcify and enlarge or diminish, usually the latter if calcification is marked; ultimately calcified abscesses may reach a state where they no longer enlarge or decrease in size and may be regarded as dormant or silent. With the escape of a lumbar abscess to the subcutaneous tissue and drainage either spontaneously or by surgery, Roentgen ray evidence usually disappears. The most serious menace to life is the lumbar abscess; its effect on the deformity is of minor importance. On the other hand, the thoracic abscess is of less danger to life but a serious menace because of its effect on the deformity.

Bronchial Obstruction: Its Relation to Atelectasis, Bronchopneumonia and Lobar Pneumonia.—From the experimental and clinical investigations of atelectasis, postoperative pneumonitis and lobar pneumonia, CORYLLOS and BIRNBAUM (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 401) conclude that they are all produced by the same mechanism, bronchial obstruction. Any interference with the free drainage of the bronchial tree will cause lesions, the nature, extent, importance and evolution of which will depend on the degree and duration of the obstruction and nature and virulence of the microbes present. The identity in pathogenesis of these conditions is proved by the gross and microscopic appearances, their bacteriology, their circulatory disturbances, their evolution and the modifications in the pulmonary gaseous exchanges occurring in them. Between them there are, in degree only, differences in local and general symptoms, roentgenographic signs and

bronchoscopic findings. The rational treatment of these conditions should be based on their etiology and, as in every other obstructive lesion, should aim to relieve the obstruction and reestablish free drainage in the bronchial tree. Lobar pneumonia is a pneumococcal bronchial obstruction with a combined atelectasis and pneumococcal cellulitis of the corresponding pulmonary area. Treatment should be directed not only against the bacteremia, but chiefly against the local or pulmonary lesion. Carbon dioxide inhalation in 5 to 10 per cent concentration seems to possess a specific action against pneumococcal pulmonary infections, and, according to experimental and clinical data, could be used both as a preventive and curative agent.

Roentgen Therapy in Acute Inflammatory Conditions.—Roentgen treatment of acute inflammatory conditions is of great help to surgery and also to more conservative methods, in the opinion of MAY (*Radiology*, 1930, 14, 411). It cannot replace old methods, but it is a very helpful adjunct to them. It not only alleviates pain, but also affects the entire process of inflammation. It should not be undertaken without proper surgical supervision. Its beneficial action is both local and general. The local effects are hyperemia, dilatation of the blood-vessels, increased circulation of the lymph and other local immunizing processes. In general, it tends to increase the specific and nonspecific forces of resistance. The optional dose of radiation lies between 130 and 300 R units on the skin over the inflamed area, using heavy filtration and high voltage. Two hundred and thirty-five cases, comprising furuncle, osteomyelitis, paronychia, pneumonia and various other acute inflammations, were subjected to Roentgen treatment by the author, and definite benefit resulted in 81.3 per cent.

Roentgenologic Diagnosis of Diseases of the Upper Respiratory Tract in Children.—PANCOAST and PENDERGRASS (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 241) hold that roentgenologic studies of the chests of infants and young children should always include the neck in order to detect possible obstructive lesions in the upper respiratory tract that may explain, wholly or in part, suspected intrathoracic conditions. The posterior border of the tongue, uvula, pharyngeal cavity and its walls, epiglottis, aryepiglottic folds, pyriform sinuses, laryngeal vestibuli, ventricular and vocal folds, and laryngeal ventricles, are easily seen in roentgenograms of the neck. Among the pathologic conditions amenable to roentgenologic diagnosis are: postdiphtheritic laryngeal stenosis, tuberculous adenitis with calcifications, retropharyngeal and retrotracheal abscess, encroachments on the nasopharynx, foreign bodies and the abnormal thymus. The stand is taken that thymic death is due largely to tracheostenosis, but is usually assisted by other factors causing upper respiratory obstruction. It is realized that much of the diagnosis of enlarged thymus is based on inadequate examination. The only definite or reliable signs of an enlarged or potentially obstructive thymus are narrowing of the trachea at the upper thoracic outlet on inspiration, too great a collapse on expiration or buckling at either phase, as shown by the lateral view, or lateral deviation of the trachea in the sagittal view. The thymus may be blamed for obstructive phenomena for which it is not responsible, and the examiner must have in

mind foreign bodies, retropharyngeal abscess, tracheal or laryngeal stenosis, recurrent laryngeal paralysis from the thymus, relaxed soft tissues of the pharynx and larynx in the young, asthma, whooping cough, meningitis and congenital cardiac conditions.

Changes Occurring in the Blood of the Newborn Following Ultraviolet Therapy.—In 50 newborn infants short exposure to the ultraviolet light increased the bleeding time and the blood platelets, according to SANFORD (*Arch. Phys. Therap., X-ray and Rad.*, 1930, 11, 101). There was no effect on the coagulation time. Short exposures to the ultraviolet light would, therefore, serve as a therapeutic measure in infants with delayed bleeding time, but their coagulation time would have to be increased by other means. Short exposure of 200 newborn infants to ultraviolet light increased the hemoglobin content and number of red cells to a slight extent in an average number of cases. In cases in which the hemoglobin content and number of red cells are lower than normal the hemoglobin and cells are increased to a greater extent, and tend to remain nearly normal. Exposure of 120 newborn infants to ultraviolet light increased the total white count to a slight extent, the lymphocytes being increased at the expense of the polymorphonuclear leukocytes. The number of young or single-lobed nucleated cells of the polymorphonuclear cells were increased. The older or multi-lobed forms were decreased. There was a rapid return to normal.

Radiant Energy as Applied to Skin Lesions.—In the view of HIGHMAN (*Arch. Phys. Therap., X-ray and Rad.*, 1930, 11, 123), a discussion of radiant energy in the treatment of skin lesions resolves itself into a comparison of the Roentgen ray with other forms of therapy. Destructive measures are superior to the Roentgen ray for neoplasms. Nothing equals the Roentgen ray, however, in treating the lymphatic infiltrations of the skin and in acne, with this reservation, that failure in so treating acne is encountered and that the lymphatic infiltrations sooner or later become unresponsive to any treatment, for they are fatal diseases. In part, the Grenz ray functions ambiguously in treating skin lesions. Radium is generally inferior to the Roentgen ray so far as skin lesions are concerned. The ultraviolet ray seems to have limited utility. Leaving out angioma serpiginosum, which is rare, and alopecia areata, in which it has some value, the ultraviolet ray does nothing that cannot be as well or better done in some other way. It does not compare with the Roentgen ray in acne or psoriasis, and has no value in the infections or neoplasms, save the Finsen ray, which stands out in the treatment of lupus vulgaris. Besides the diseases mentioned, epithelioma, particularly the basal-cell type, sarcoma of Kaposi, other sarcomata, the lymphodermas, mycosis, psoriasis, lichen planus and other scaling dermatoses are all amenable to the Roentgen ray. The infections more or less amenable to this ray are sarcoid and granuloma annulare, lupus vulgaris, rhinoscleroma, actinomycosis, perhaps blastomycosis, furunculosis and some forms of tinea. An unexplained phenomenon is the antipruritic action of the ray in some cases of vulvar and anal itching. The Roentgen ray is also used to produce epilation in tinea of the scalp. Permanent alopecia, as for hirsuties, should not be attempted.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

The Relationship of the Psychiatric Clinic to the Juvenile Court.

—PLANT (*Ment. Hyg.*, 1929, 13, 708) reviews the history of psychiatric advice in court work, beginning with Dr. William Healy's efforts in the Chicago Juvenile Court and its gradual spread. He calls attention to the fact that the physician's point of view is that of the individual, whereas the court's point of view is that of the community or of society. For this reason he considers that the court and the psychiatrist must always be opposed to each other, and that this is a healthy condition. The aim of the court is to see that society is protected, and the aim of the psychiatrist is to see that the individual factors are fully presented to the court. He cites a number of cases to demonstrate that many of the more or less serious social problems express a conflict between the needs of the individual and the needs of society and that many of the problems arise directly because we do have normal people in a normal social environment. He believes that the court and the psychiatrist will mutually increase the difficulties of the other. "To the judge now, and for the future, belongs the social responsibility and final disposition of all the data. We have little patience with any notion that this work should be taken out of legal hands even in the Juvenile Court. Our progress must ever rest upon the solidarity of our social institutions. Tugging and straining at this leash is always individual initiative, growth and idiosyncrasy. In our total social structure that is a necessary element. To present its fullest claims before the court, the psychiatric clinic exists. Our recommendations assume for the moment the paramount interests of the child, as if the whole world were to be built about his needs. It is, and will be, for the Juvenile Court to take these recommendations for review and replacement in the light of the needs of the solidarity and progress of our social institutions."

Predictability in the Administration of Criminal Justice.—GLUECK and GLUECK (*Ment. Hyg.*, 1929, 13, 678) present a real contribution to criminologic research in this paper. The ideas in the article are taken from one chapter of the recently published book by the same authors, *Five Hundred Criminal Careers*. The authors call attention to the fact that the efforts to predict on the basis of statistical indices the recurrence of crime in individuals which have formerly been attempted have been subject to a number of faults which render them unreliable. They find that the usual reports of recurrence of criminality are far too low.

In their own study they found that only 20 per cent of the graduates of one of the better American reformatories have abandoned their lives of crime. To present sufficient data for an understanding of the tables and the method of derivation is beyond the scope of an abstract. The authors present evidence to show that the offense for which the person was sent to the reformatory has no bearing on the final outcome of the career. They offer four prognostic tables, the first of which is derived from an evaluation of the six most important pre-reformatory factors in the life of the criminal. They derive figures which should at least serve as an approximation of the probability of correction of criminality at the time that a judge is considering sentence to a reformatory. The second table is devised for use in considering parole from a reformatory and is based upon the six highest pre-reformatory factors and the highest reformatory factor (that is, that factor in the reformatory career which is most closely correlated with subsequent failure of parole). The next table is derived from the consideration of the pre-reformatory factors, the highest reformatory factor and the highest factor in parole life. It is designed for the determination of whether a criminal who has been on parole should be discharged or whether he should be continued under parole supervision. The fourth table adds to these former factors the five highest post-parole factors. It is easily seen that as new factors are added to the indices the degree of accuracy in predictability increases and this is exhibited by the actual facts of the tables. They present a sample of the application of this sort of prognostic procedure to actual criminal cases. The authors do not intend that these tables should be adopted immediately by the judiciary, but suggest some such prognostic method be worked out and tried out practically with a view to correcting its defects with the ultimate aim of attaining a prognostic instrument which could give a definite degree of probability in determining the disposition of criminal cases at any time that a change in the handling of that individual becomes necessary. In our opinion, the authors have made a distinct advance in this field.

Suggestions as to the Detection and Treatment of Personality Difficulties in College Students.—ESTABROOKS (*Ment. Hyg.*, 1929, 13, 794) presents a development of mental hygiene at Colgate University, where they do not have a psychiatrist to carry on the work. This presentation must be of importance at the present time as the majority of our colleges and universities either do not have funds for psychiatric assistance in this work or are unable to obtain competent men to carry it on. The author calls attention to this and proceeds to tell us how the problem is handled at Colgate. All college freshmen are required to take the intelligence test for a college freshman as prepared by the American Council on Education. They fill out a vocational-interest blank and are given the Colgate tests for the detection of psychoneurotic traits and for introversion and extroversion. They have found that troubles of adjustment occur in the lower tenth of the intelligence scores and in the higher tenth of the psychoneurotic scores. The students in the first group (of low intelligence) are seen in the week after the opening of college. They are told frankly of their handicap, given some reassurance and encouraged to do their best. The group comprising the upper tenth in the psychoneurotic test are seen in the first or second

week of the term, usually under some fictitious reason. An attempt is made at this time to estimate the nervous stability of the student. From both of these groups those individuals who appear to be particularly susceptible to behavior disorders are selected out for further study. After these are disposed of, every member of the freshman class is interviewed for the purpose of vocational and educational guidance and at the same time a consideration is given to the mental hygiene viewpoint. While the majority of problems are revealed by these methods, some are overlooked. It is the practice at Colgate to confer with the teachers in rhetoric and debating, religion and ethics, because they have found a personality defect to show up quite frequently in these courses. Also use is made of faculty meetings where instructors are requested to report any queer students to the personnel department. Also a number of the freshman class who appear particularly stable are requested to keep an eye open for those students who are not making a good adjustment and to report them to the personnel department. The author recognizes the fact that a psychiatrist should be available for every problem case. "We should have a high grade psychiatrist on every problem case; only, in the first place, there are not enough Healys and Bronners to go around as has been pointed out before. Secondly, most institutions cannot afford such luxuries just at present. So we get on with what we have and pray for a better day to come." He points out that much can be done even in the absence of a psychiatrist.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis.—CECIL, NICHOLLS and STAINSBY (*Arch. Int. Med.*, 1929, 43, 571) isolated a streptococcus from the circulating blood of patients with chronic infectious arthritis in 61.5 per cent of 78 cases. Of these streptococci, 83.3 per cent are culturally and biologically identical, and appear to be attenuated hemolytic streptococci. This dominant strain has been called the "typical strain." The remaining strains fall definitely into either the viridans or the indifferent group of streptococci. A streptococcus, culturally and biologically identical with the strain isolated from the blood, can sometimes be cultivated from one of the affected joints in the same patient. A streptococcus, culturally and biologically identical with the strain isolated from the blood and joints,

can sometimes be isolated from a focus of infection in the same patient. When the "typical strain" of streptococcus is injected intravenously into rabbits, a majority of the rabbits develop a chronic nonsuppurative polyarthritis. Microscopically, the histologic changes in the rabbit's joints are practically identical with those observed in the joints of patients with chronic infectious arthritis. Cultures from the blood and from the joints of rabbits infected with experimental arthritis frequently yield a streptococcus identical with the strain originally injected. These observations tend strongly to confirm the theory that chronic infectious arthritis is a streptococcal infection, caused in a large proportion of cases by a biologically specific strain of this organism. The presence of this specific strain of streptococcus in the blood of several patients with advanced arthritis deformans goes far to corroborate the view already widely held that arthritis deformans and chronic infectious arthritis are one and the same disease. The same authors studied the bacteriology of the blood and joints in rheumatic fever (*J. Exper. Med.*, 1929, 50, 617). During the spring of 1928, 29 patients with acute rheumatic fever were subjected to blood cultures, of whom 9, or 31 per cent, yielded a streptococcus. During the spring of 1929, 31 patients with acute rheumatic fever were studied by blood cultures, of whom 26, or 83.9 per cent, yielded a streptococcus. The higher percentage of positive cultures in the 1929 series appears to have been due to improved cultural methods. Of the 35 strains of streptococci recovered from blood cultures, 33 have been classified as alpha streptococci (*Streptococcus viridans*); one as a beta streptococcus (*Streptococcus hemolyticus*); and one a gamma streptococcus (*Streptococcus anhemolyticus*). Some of the viridans strains produced very little green on blood media. Agglutination and absorption tests indicate that the strains of *Streptococcus viridans* recovered from the blood of patients with rheumatic fever show a tendency to fall into specific biologic groups. In 7 patients with rheumatic fever who were subjected to cultures from affected joints, 5, or 71.4 per cent, yielded a *Streptococcus viridans*. In 3 patients in whom green streptococci were recovered from both the blood and joint, agglutination and absorption tests proved the identity of the strains isolated from the two sources. These findings corroborate those of previous investigators and make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection usually of the *alpha* or *viridans* type. The pathogenesis of rheumatic fever in respect to the joint lesions appears to be analogous to that of infectious arthritis and gonococcal arthritis. Bacterial allergy probably influences the clinical picture in all three conditions, but in each instance the joint manifestations are primarily dependent upon localization of bacteria in the joint, with subsequent infection.

Current Malaria Studies, with Special Reference to the Control Measures.—WILLIAMS (*Pub. Health Rep.*, 1929, 44, 2001) notes that malaria has become more severe and has increased in amount in the southern states in the last few years, especially in 1927 and 1928. Some cases of the more severe forms of infection, hematuria, algid and cerebral, have occurred. Blood examinations have shown some very high rates, even up to 45 per cent. Most control work has been urban though rural infections have always been heavier. The cost of control

measures in rural areas is heavier than in urban. Quinin prophylaxis has not proven very effective but plasmochin is more promising and it is suggested that the inclusion of this drug in chill tonics would be advantageous. Screening is regarded as the sheet anchor of success and it can be carried out for as little as \$8.00 per house. Another line of attack is in the use of Paris green as an anopheline larvacide.

Typhus Fever in the United States.—MAXCY (*Pub. Health Rep.*, 1929, 44, 1735) presents a review of the subject, and the following discussion and summary: The evidence thus far adduced indicates that there is endemic in the United States a disease which is clinically indistinguishable from the mild typhus occurring during interepidemic periods in the Old World and in Mexico. The relationship of this disease to typhus is further borne out by serologic similarities. The Weil-Felix reaction is positive. The value of this observation in establishing the relationship of the disease in this country with that of the Old World has been modified by the recent discovery (Kerlec and Speneer), 1929 that the Weil-Felix reaction is positive in Rocky Mountain spotted fever, a disease which, though it belongs to the typhus group, is immunologically distinct. Observations in experimental animals are interpreted as meaning that the endemic typhus of the United States has common origin with the "tabardillo" of Mexico. The typhus which has been occurring in our eastern seaports does not depend upon direct importation from across the sea. It belongs to the North American Continent. In addition to the peculiarities of the virus, the disease in this country manifests certain epidemiologic characteristics which are in contrast with those generally attributed to the typhus of the Old World. They relate principally to the mode of transmission. These considerations have led to a tentative rejection of the human louse as the principal vector and of man as the principal reservoir of the disease in this part of the United States and the search for some other mode of transmission. In typhus fever it has been shown by Nicolle and others that beside the chimpanzee and the monkey certain small rodents are susceptible to the virus; that is, guinea pigs, rabbits, rats (white and gray), mice (white), and the gerbille. In a recent publication Nicolle (1926) reports a second series of passages of typhus virus through 12 generations of white rats. The question arises whether in the endemic typhus of the southeastern United States a reservoir of the disease may not exist other than in man, a rodent reservoir with accidental transmission to man through the bite of some parasitic bloodsucking insect or arachnid. Such a hypothesis is compatible with the epidemiologic characteristics which have been presented, namely: (1) The uneven focal distribution of the disease; (2) its sporadic occurrence; (3) its apparent lack of direct communicability from an infected person; (4) its association with the place of business rather than with the home, particularly with those premises upon which foodstuffs are handled or stored; (5) the recurrence of cases on the same premises after considerable intervals of time; (6) its seasonal incidence. Obviously, the rodents upon which suspicion immediately falls are rats and mice, and the parasitic intermediaries which are first suspected are fleas, mites, or possibly ticks. In summary, there is endemic in the United States a disease which resembles typhus and gives a positive Weil-Felix reaction. The virus of this disease has been identified with that of "tabardillo" in Mexico,

and both have been shown to be closely related to the virus of Old World typhus by immunologic tests. The North American strain appears to be originally derived from Old World sources. The epidemiology of the typhus of the United States is not compatible with man-to-man transmission by the louse. It suggests the existence of some other mechanism for the propagation of the virus. From a consideration of what is known of this group of diseases, the "rickettsias," and specifically with regard to the susceptibility of rodents to typhus virus, it seems probable that a reservoir may exist apart from man. A reservoir in rats or mice, with accidental transmission to man through the bite of some bloodsucking parasite, would be consistent with the known facts.

Septic Sore Throat.—DAVIS (*J. Am. Med. Assn.*, 1929, 93, 978) claims that the present status of the epidemiology of septic sore throat is much the same as it was twenty years ago. Outbreaks are rare. They occur here and there and probably will continue to do so. No doubt, epidemics are now being observed that years ago would not have been recognized. Modern methods of pasteurization and the careful supervision of certified milk products, together with new methods of identifying *Streptococcus epidemicus* should do, and possibly have already done, much to prevent epidemics. Much still remains to be done, however, in the control of milk supplies before the disease can be completely eradicated.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Variation of Response to Infection with *Treponema Pallidum* Between an Albino and a Brown Breed of Rabbit.—The evidence presented by FRAZIER and MU (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 243) indicated that albino rabbits were less resistant to infection with *Treponema pallidum* than were the brown breed. This was shown by extent and duration of the orchitis and the incidence of metastatic keratitis. The albino rabbits during the period of the most active clinical lesions were in poor general condition, being less active and showing changes in their hair, while the brown animals remained vigorous and well groomed.

The Local Effect of the Injection of Gases into the Subcutaneous Tissues.—The introduction of various gases into tissues and cavities has been carried out for many years in experimental studies, and in human cases for therapeutic purposes. The observations which were recorded in respect to these studies deal with the clinical signs, while none of them have indicated the reaction occurring in the tissues in

consequence to the presence of the foreign gas. However, Wolbach noted the tissue response arising through the presence of air in cases of interstitial emphysema associated with influenza. Recently, WRIGHT (*Am. J. Path.*, 1930, 6, 87) studied the effect of a variety of gases when introduced into the tissues. He found that the subcutaneous injection of oxygen, nitrogen and carbon dioxide led to an inflammatory reaction with the presence of monocytes, epithelioid cells and giant cells, as seen in granulomata. The reactions are nonspecific, the monocytes, he believes, arise locally from some type of fixed connective-tissue cell, while the giant cells arise from the same source. Histologic studies resembling tubercles have been found quite commonly, and a fibrinous deposit is not infrequently seen within the gas spaces. These spaces become lined by mesothelial-like cells within six to eight days.

Lymphogranulomatosis of Lung.—WEBER (*Ziegler's Beitr. f. Path. Anat.*, 1930, 84, 1) discusses 7 cases of Hodgkin's disease which had involved lung. Three of these cases appeared to have their beginning in the lung structure, while 4 others were located within the thoracic glands and had secondarily invaded the lung. Only one of these cases was correctly diagnosed clinically, while one was diagnosed by microscopic sections during life. In the remaining group a diagnosis of tuberculosis was usually offered, and in one case was found at autopsy to be present along with the nodules of Hodgkin's disease. The granulomatous masses may be small and local, or may involve the whole lobe. Occasionally multiple, small nodules are scattered through several lobes. The process of necrosis may be more pronounced in Hodgkin's disease of the lung than is usually noted in the lymphatic glands. Cavities may be formed. The structure of the granulomatous mass simulates that encountered in other tissues. The author found that radiation inhibits somewhat the progress of the lesion. The granulomatous mass may give rise to small nodular processes in the intima of vessels. These nodules may develop to obstruct the lumen.

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ORIGINAL ARTICLES.

OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF
ACHYLIA GASTRICA TO PERNICIOUS ANEMIA.*

III. THE NATURE OF THE REACTION BETWEEN NORMAL HUMAN
GASTRIC JUICE AND BEEF MUSCLE LEADING TO CLINICAL
IMPROVEMENT AND INCREASED BLOOD FORMATION SIMILAR TO
THE EFFECT OF LIVER FEEDING.†

BY WILLIAM B. CASTLE, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, AND ASSOCIATE
PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL,

WILMOT C. TOWNSEND, M.D.,

FORMERLY ASSISTANT IN TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT
RESIDENT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, AND RESI-
DENT PHYSICIAN, TROPICAL MEDICAL SERVICE, BOSTON
CITY HOSPITAL,

AND

CLARK W. HEATH, M.D.,

ASSISTANT IN MEDICINE AND TROPICAL MEDICINE, HARVARD MEDICAL SCHOOL; ASSIST-
TANT RESIDENT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, AND
RESIDENT PHYSICIAN, TROPICAL MEDICINE SERVICE, BOSTON
CITY HOSPITAL.

(From the Thorndike Memorial Laboratory of the Boston City Hospital, and the
Department of Medicine, Harvard Medical School.)

It has been demonstrated by the experiments reported in the first two papers of this series^{1,2} that the normal human stomach, by virtue of its content of secretions, can produce by an interaction with beef muscle a substance effective in a fashion similar to liver in promoting prompt blood regeneration and clinical improvement in Addisonian pernicious anemia. Since this function of the con-

* An essay containing the subject matter of the two preceding papers of this series (I and II) and of the first section of this paper, by William B. Castle and Wilmot C. Townsend, was awarded the Warren Triennial Prize of the Massachusetts General Hospital for 1928.

† The expenses of the present investigation were borne in part by grants from the J. K. Lilly gift to the Medical School of Harvard University.

tents of the normal stomach was shown to be in contrast to the inability of the patient with pernicious anemia to produce such an effect from ingested beef muscle, a critical analysis of this process becomes essential to a further comprehension of the nature of the disease. The source of the constituent of the gastric contents active in the production of those effects was the liquid removed from the stomachs of healthy fasting subjects during the hour subsequent to the subcutaneous injection of 0.5 mg. of histamin phosphate.³ The other constituent of the effective reaction as previously described was lean-beef muscle divided as finely as possible with a special meat chopper. In preparing the materials for incubation 200 gm. of the beef muscle were carefully mixed with from 150 to 300 cc. of the fasting gastric contents and brought to a temperature of 37.5° C. while hydrochloric acid (usually from 5 to 10 cc. of a two-thirds concentrated solution) was added until the reaction of the material was just distinctly orange to Töpfer's reagent (pH 2.5 to 3.5). The mixture was then kept in the incubator for two hours with occasional stirring and the addition of a few drops of acid to maintain a relatively constant acidity. The material was then removed from the incubator, passed through a wire strainer and strong sodium hydroxid added until a pH value of 5 was obtained. It was then given daily, usually within half an hour, to the fasting patient by means of a nasal tube introduced into the stomach, and no food was taken by the patient for at least an hour thereafter. It is therefore evident that the process freely permits an interaction between a factor present in the normal gastric juice, which may thus be termed intrinsic, and a factor contained in the beef muscle, which is thus an extrinsic element.

Analysis of the Nature of the Intrinsic Factor. Since the outstanding difference between the digestive tract of the patient with pernicious anemia and that of the normal individual is the inability of the stomach of the former to secrete hydrochloric acid⁴ or pepsin,⁵ and since the environment, at least in the *in vitro* phase of the conditions under which normal fasting human gastric contents secreted after histamin stimulation have been shown to create the effective substance, is such as to promote peptic digestion, it appeared possible that peptic hydrolysis was the intimate nature of the process leading to the production of the effective agent. However, after the partial neutralization with the sodium hydroxid, and after introduction into the gastrointestinal tract of the patient, a potentially significant *in vivo* phase began, in which opportunity might have been afforded for the saliva or bile occasionally contaminating the gastric juice of the normal individual to interact effectively with the beef muscle or for a different action of the gastric juice upon the beef muscle to take place. The negative experiments with fasting gastric contents alone, obtained after

histamin injection² (Cases 11, 19 and 24), indicate no possibility of direct hematopoietic action by any of the constituents of the normal gastric contents, but only of their indirect action upon the beef muscle. It appeared desirable, therefore, to eliminate certain of these possibilities at once by an attempt to reproduce with the use of purer sources of peptic activity the effects seen with fasting normal gastric contents.

A series of experiments will now be described as performed upon cases of classical Addisonian pernicious anemia. The ward diets utilized contained no red meat, liver or kidneys. The blood studies were carried out as already described,¹ and the criteria of activity in promoting blood formation were those clearly defined by Minot and his associates^{6,7} and previously shown to be applicable to those experiments.¹ A positive effect was considered to be indicated by a significant response of reticulocytes within ten days after the beginning of the uniform daily administration of the material to be tested. This was always associated with clinical improvement and eventually in most instances by an increase of over 1,000,000 red blood cells per cubic millimeter. Conversely, a negative effect was considered to be indicated by the absence of a significant increase of reticulocytes within a period of ten days. In the tables the data are given for alternate days only during the administration of the test preparations.

(a) *The Effect of the Incubation of Beef Muscle with Pepsin in the Presence of Hydrochloric Acid.* Pepsin (U.S.P.) is available in the form of dry, yellowish granules. It is prepared by the autolysis of the mucous membrane of the pig's stomach in the presence of hydrochloric acid,⁸ and is actively proteolytic in acid solution. A solution of this substance in dilute hydrochloric acid was therefore used, instead of normal human fasting gastric contents recovered after histamin stimulation, during the incubation of the beef muscle in observations on 3 patients. Two hundred grams of beef muscle were mixed in a beaker with from 100 to 200 cc. of warm tap water in which had been dissolved from 2 to 5 gm. of the pepsin. While the temperature of the mixture was being brought to that of the incubator, strong hydrochloric acid was added until the reaction of the mixture was slightly orange to Töpfer's reagent (pH 2.5 to 3.5). The material was then incubated for from two to twenty-four hours in different experiments, the resulting liquid passed through a wire strainer, neutralized to pH 5 and administered to the fasting patients exactly as was done in the experiments with the gastric juice as a source of peptic activity. Table I shows the results of this therapy in the control periods of the 3 cases so treated (Cases 9, 10 and 21). It will be noted that in none of these patients was there the slightest evidence of an effect on either reticulocytes or the total number of red blood cells, although in the subsequent test

periods of Cases 9 and 10, excellent remissions were induced with the gastric contents of normal individuals recovered after they had ingested beef muscle.¹ In Case No. 21, liver extract given later yielded a satisfactory remission.

In the observations on a fourth case (Case 20) (See Table I) there was conducted for another purpose an even more convincing experiment, since in this case the environment for the activity of the pepsin was actually normal human gastric juice inactivated in terms of these experiments by previous heating to from 70° to 80° C. for a half hour. The endowment of this inactivated gastric juice during the control period with proteolytic ability provided by the pepsin was found to be an unsuccessful substitute for the original essential activity of the unheated gastric juice clearly demonstrable in the subsequent test period. The experiments carried out on 2 other subjects (Cases 23 and 34), designed primarily for other purposes demonstrate incidentally in the control periods the negative action of pepsin and hydrochloric acid, and also in the subsequent test periods its inability to produce an inhibitory effect on the usual action of normal human fasting gastric contents obtained after histamin stimulation. It must be concluded, therefore, from the behavior of these 6 cases, that peptic hydrolysis by means of pig pepsin is incapable of duplicating the results seen with human gastric juice. This at that time somewhat surprising negative result has already been briefly reported^{9,10} and has since been confirmed by Wilkinson.¹¹

(b) *The Effect of the Incubation of Beef Muscle with Normal Human Gastric Juice Rendered Proteolytically Inactive by Heat.* Since an unexpected obstacle to the direct proof of the assumed importance of peptic hydrolysis had been encountered in the failure of the experiments with pig pepsin, it became necessary to attempt to adduce indirect evidence for the possible significance of peptic hydrolysis or a related enzyme process taking place with human gastric juice. If it could be shown that when the enzymes of the gastric juice were rendered inactive the effect was not obtained evidence at least consistent with the idea of an enzyme action would be obtained. Accordingly, the usual technique of *in vitro* incubation of 200 gm. of beef muscle with 150 cc. of human gastric juice was employed, with the exception that the gastric juice was first heated on a water bath for a half hour at a temperature between 70° and 80° C., and then rapidly cooled to 37.5° C. before incubation with the beef muscle. This, as was shown with Mett's tubes, effectively destroyed all peptic activity. However, in order to be certain that the physical aspects of the digestion were carried out, 2 gm. of pepsin were added to the mixture immediately before its incubation. It was, of course, already known from three of the experiments just reported that this substance, though proteolytically active, was incapable of producing the effective principle from

beef muscle. After neutralization to pH 5, the incubated material was given to Case 20 for a period of ten days with the entirely negative result, shown in the control period (Table I). The procedure was now changed during the test period of this patient only by using unheated gastric juice. The pepsin was added in order to be certain that it could not have acted in some way as an inhibitor to the production of the active principle in the procedure of the control period. An excellent remission was promptly obtained, with a maximum production of reticulocytes of 19.6 per cent on the eighth day at an initial level of 2.28* million red blood cells per cubic millimeter, and a gain of over a million red blood cells per cubic millimeter during the eighteen days of this treatment. It is then clear that the heating of the gastric juice was the cause of the failure of any effect to appear in the control period of this case.

Since the peptic activity of the gastric contents was destroyed by heating, the experiment is entirely consistent with the idea of the indispensability of the peptic hydrolysis of protein for the production of the effective substance. Despite the negative effects with pig pepsin it still seemed possible that the negative effect was due to the destruction of the human pepsin, the chief proteolytic enzyme of the human gastric juice, particularly as the chief constituent of the beef muscle used in these experiments was protein. If, however, the action of the human pepsin were assumed to be the basis of the positive effects seen with the fasting gastric contents, the negative effects in the experiments with the pepsin of the pig would have to be explained by a difference in the sources of pepsin. On the other hand, the difference between the action of pig pepsin and of human gastric juice might indicate that the effective intrinsic factor of the latter was not secreted by the human gastric mucosa, and hence was not found in the preparation made from the homologous organ of the pig. It appeared logical, therefore, next to attempt to narrow down the possible sources of the effective substance acting as the intrinsic factor in the positive reactions with human gastric contents. The unavoidable presence of saliva and the occasionally regurgitated duodenal contents in the gastric juice as used made it impossible to be certain that the intrinsic effective substance was secreted by the normal gastric mucosa. The probability that this was so, particularly in view of the well-known clinical pathology of the stomach in pernicious anemia, appeared to be great; but absolute proof was lacking by this use of gastric juice representing secretions other than those of the stomach wall itself.

(c) *The Effect of the Incubation of Beef Muscle with Normal Human Saliva.* Accordingly, it was decided first to test the possible rôle of the normal salivary action in these experiments. In order to give an optimum chance for effect of the saliva to display itself,

* For convenience in referring to the tables the red blood cell count of the second day of the test period is taken as the initial figure.

200 gm. of beef muscle were carefully chewed by one or more healthy normal subjects and expectorated into a beaker which was then placed in the incubator for one hour. No change in the physical appearance of the beef muscle occurred during this time. To this material was now added from 150 to 200 cc. of warm tap water, 3 gm. of pepsin and enough strong hydrochloric acid to give a pH of from 2.5 to 3.5. After thorough mixing, the material was incubated for two hours and given daily to Case 23, immediately after neutralization to pH 5. As it was already known from the experiment with heated gastric juice (Case 20) that the pepsin could neither cause nor inhibit an effect if produced by another constituent, this conduct of the control period of the experiment would certainly give the saliva both before and after encountering the acid-pepsin mixture, an opportunity to act presumably even better than that afforded to the swallowed saliva ordinarily present in the gastric contents. In Table I data are presented which show the entirely negative effect of this procedure during the control period of Case 23. A prompt effect appeared during the test period when the only change in the procedure consisted of the substitution of fasting human gastric contents for the water used in the control period. The resulting remission was characterized by a maximum production of reticulocytes on the eighth day of 12.8 per cent, and an increase of the red blood cell count from 1.90 to 3.05 millions per cubic millimeter within twenty days. The pepsin was again shown to have no effect in inhibiting the production of the effective substance, and the salivary activity, even under optimum conditions, was demonstrated to have played no part in the process.

(d) *The Effect of the Incubation of Beef Muscle with Normal Human Duodenal Contents.* It now remained to determine whether the small amounts of duodenal secretions occasionally obtained with the fasting gastric contents had been operative in the production of the effective substance. This seemed a remote possibility because of the fact that bile was by no means regularly present in the gastric contents and had been rarely encountered in the contents of the normal stomachs recovered after the ingestion of the beef muscle. Furthermore, the enzymes of the duodenum of patients with pernicious anemia are ordinarily found to be normally active.¹² Since at the acid reactions utilized in the *in vitro* incubations with gastric juice the enzymes of the duodenum could hardly have been active^{13,14}, the phase of the process in which such activity might have been manifest was presumably that following the administration of the material to the patient subsequent to neutralization to pH 5. It therefore seemed proper to test the effect of the duodenal contents near the neutral point and a reaction of pH 7 was chosen for the *in vitro* incubation and subsequent administration to the patient. This conduct of the experiment was also apparently necessitated by another difficulty inherent in the usual methods available for col-

lecting human duodenal contents, for by means of a simple duodenal intubation it obviously would be impossible to collect duodenal contents completely free from gastric juice. If, then, the incubation were carried out at an acid reaction, it would be impossible to exclude the possibility of the participation of the pepsin of the gastric juice recovered with the duodenal contents. On the other hand, because none of the patients so far had received material at any other acidity than at pH 5, in the event of a negative result it would be necessary to prove subsequently the effectiveness of the products of the incubation of the beef muscle with gastric juice when administered to the patient at the neutral point.

The subjects furnishing the duodenal contents were healthy medical students in the fasting condition. The duodenal contents collected each day from one subject were used that day for one patient in the observations to be described. A duodenal tube was swallowed and the tip allowed to enter the second portion of the duodenum where its position was checked by fluoroscopic examination. The subject was then given about 30 cc. of olive oil by mouth to promote secretion, and the characteristic golden-brown contents of the duodenum collected over a period of about an hour. The material had usually a reaction of about pH 7 or if slightly acid was brought to that point with a little sodium hydroxid and at once placed in the icebox. In this fashion, about 150 cc. of duodenal contents containing a little olive oil were obtained daily. The customary 200 gm. of beef muscle were brought to pH 7 with strong sodium hydroxid and then thoroughly mixed with the duodenal contents at the same pH, while the temperature of the mixture was being brought to 37.5° C. After an incubation period of two hours the material was again brought to pH 7 with a few drops of strong sodium hydroxid, passed through a wire strainer and administered each day to the fasting patient for a period of ten days.

An inspection of the data for Case 28 presented in Table I suggests that an effective interaction took place between the duodenal contents and the beef muscle during the control period, since at the relatively high initial red blood cell level of 2.5 million per cubic millimeter, a maximum production of 5.1 per cent of reticulocytes appeared on the eighth day. In order to determine whether or not this was a maximum effect for this procedure, in the immediately following ten-day test period 200 gm. of beef muscle were incubated in the ordinary manner with 150 cc. of normal gastric juice at pH 2.5 to 3.5 and given daily to the patient after neutralization to pH 5. It will be seen that there was no secondary rise of reticulocytes, a fact which may be taken to indicate that this procedure was incapable of producing detectably more of the effective substance than was the interaction of the duodenal contents and the beef muscle at pH 7. This positive result with duodenal contents appeared so contrary to expectation that the experiment was carried out on

Case 32 in essentially the same way, except that in the test period the beef muscle was first liquefied by incubation with pepsin at pH 2.5 to 3.5 for two hours and then after neutralization to pH 7 was incubated for two hours with gastric juice obtained with great care free from duodenal contents. The material was also administered to the patient at pH 7. As with Case 28, the interaction of the duodenal contents and beef muscle at pH 7 gave evidence of the formation of an effective substance resulting on administration to this patient at an initial red blood cell count of 1.66 million per c.mm. in a maximum production of 12.4 per cent of reticulocytes on the tenth day of the treatment. In the subsequent test period, incubation of the beef muscle with 5 gm. of pepsin at pH 2.5 to 3.5, followed by incubation with fasting gastric juice at pH 7 caused no second rise of reticulocytes and thus gave no indication of a greater production of the effective principle. There was no doubt, therefore, that these normal duodenal contents, containing some gastric juice, even though incubated and administered at a neutral reaction, could produce the effective principle in amounts not detectably less than those produced with gastric juice.

The obvious explanation of this phenomenon, that the reaction was due to the action on the beef muscle of some factor or factors in the duodenal contents other than gastric juice, seemed unsatisfactory because of the known pathologic physiology of the gastrointestinal tract in pernicious anemia. It has been shown that in contrast to the defective enzyme activity of the stomach of these patients,⁵ the enzymes of the duodenal contents are ordinarily found to be normally active.¹² Furthermore, the basis of all the effects previously seen with the normal human gastric contents could hardly have been the presence of variable small amounts of regurgitated duodenal contents; and if so, it was difficult to see why the apparently normal duodenal contents of the pernicious anemia patient could not effectively produce from the feeding of beef muscle alone a sufficiency of the effective principle. That this was not possible was clearly demonstrated¹ in the observations during the control Cases 1, 4 and 10. In these early experiments it was shown that between 200 and 300 gm. of finely-divided beef muscle fed daily to patients with pernicious anemia were totally ineffective in terms of these reactions. However, a second possibility was that since the normal duodenal contents contained much bile just derived from the liver of a normal individual, a portion of the liver extract content of that organ might have been excreted with the bile and so be the basis of the effects seen in these particular experiments. This, however, seemed in all probability excluded by the negative effect of the daily administration for ten days of the material resulting from the incubation of 150 cc. of normal duodenal contents with an indifferent protein preparation in the control period of Case 29, shortly to be described. (See Table II.)

TABLE II.—RESULTS OF ADMINISTERING TO 5 CASES OF PERNICIOUS ANEMIA BEEF MUSCLE PROTEIN AFTER INCUBATION WITH NORMAL HUMAN GASTRIC JUICE.

Control Periods.

Daily administration of various substances as indicated below.

Days of treatment.	No control.		No control.		Gluten flour 100 gm. incubated with gastric juice.		Protein from beef muscle 200 gm. incubated with duodenal contents.		No control.	
	CASE 25.		CASE 26.		CASE 27.		CASE 29.		CASE 35.	
	R.B.C. (mils.).	Retic. (%)	R.B.C. (mils.).	Retic. (%)	R.B.C. (mils.).	Retic. (%)	R.B.C. (mils.).	Retic. (%)	R.B.C. (mils.).	Retic. (%)
0	1.33	1.8	1.37	0.6
2	1.46	1.6	1.26	0.6
4	1.13	1.4	1.14	1.4
6	1.21	1.3	1.20	2.3
8	1.16	1.2	1.29	2.1
10	1.28	1.8

Test Periods.

Daily administration of substances as indicated below.

Protein free of fat and carbohydrate precipitated at pH 6 from 200 gm. beef muscle incubated with gastric juice.										
2	1.31	2.6	1.81	1.2	1.01	1.6	1.32	1.0	1.51	1.0
4	1.21	2.0	2.10	3.0	0.97	3.2	1.20	1.0	1.24	1.0
6	1.21	3.6	2.14	3.6	0.95	4.3	1.27	3.0	1.17	2.6
8	1.45	15.1	1.80	7.4	0.74	6.2	1.41	2.0	1.29	9.9
10	1.84	23.3	1.90	9.6	0.91	11.4	1.30	2.2	1.60	5.8
12	1.78	12.0	2.24	7.4	10.8	1.38	5.1
14	2.28	10.4	2.18	3.4	Patient had infection		Subsequent good response to liver extract		Patient had cystitis	
16	2.59	4.8	2.41	4.8						
18	2.60	2.8	2.60	2.0						
20	2.38	2.2						
22	2.61	1.4						
24	2.76	3.2						
26	2.86	2.6						

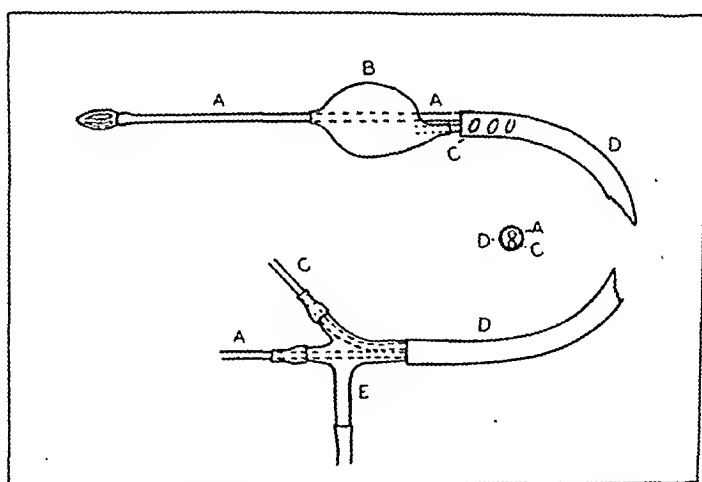
The third possibility was that the effects seen were in reality due to gastric juice necessarily present in the duodenal contents as collected by the simple technique described. This had been regarded as excluded by the fact that since the materials were incubated at a more alkaline reaction than is compatible with the proteolytic action of pepsin, the influence of this or other enzymes capable of acting only in an acid medium could be avoided. If, however, the essential reaction was not due to such enzymes, and thus could take place in a neutral environment, a technique for collecting duodenal contents, which obviously permitted gastric secretion to

enter the duodenum, would be worthless in examining the effectiveness of duodenal contents alone. Indeed, considerable gastric juice was readily demonstrated in these duodenal contents, for by means of Mett's tubes it was found that these secretions when rendered acid had a pronounced proteolytic action. Moreover from the evidence of the control periods of Cases 15 and 16 heretofore described² it could possibly be inferred that some effective interaction between gastric juice and beef muscle could take place at an acidity at least no greater than pH 5. It was at this reaction that these substances were administered separately to these two patients, but with the production of remissions, nevertheless, which were considered as probably due to the impossibility of completely preventing contact between the gastric juice and beef muscle within the patient. In order then to test the possibility that gastric secretions included in these duodenal contents might be the basis of the observed effects, it was decided first to test the influence of gastric contents collected entirely free from duodenal contents and then incubated with beef muscle at pH 7, and, second, if this gave a positive result to collect by a special technique duodenal contents free if possible from gastric juice.

(e) *The Effect of the Incubation of Beef Muscle with Normal Human Gastric Juice Containing no Duodenal Contents (in Neutral Solution).* The first of these experimental maneuvers was carried out on Case 33 with the results shown in Table I. Gastric juice was collected from normal subjects in the usual manner except that before the injection of histamin the fasting contents were discarded and the stomach washed with water to remove all traces of bile. After the subcutaneous injection of 0.5 mg. of histamin the juice secreted was removed with a syringe at frequent intervals and only colorless gastric juice saved. In this way the presence of regurgitated duodenal contents was obviated. Two hundred grams of beef muscle were incubated for two hours in the presence of 5 gm. of pepsin and 80 cc. of water at a pH of from 2.5 to 3.5 maintained by appropriate additions of strong hydrochloric acid. The resulting liquid was then neutralized to pH 7 with strong sodium hydroxid and to it were added from 150 to 200 cc. of the gastric juice collected as described above, which had itself been neutralized with sodium hydroxid. The mixture was next incubated for two hours and then given daily at pH 7 to the fasting patient. Since the patient had achylia gastrica it was, of course, impossible for the material at any time to become significantly acid, and any effects seen must have been due to the action of the gastric juice on the beef muscle either within the incubator or the patient's gastrointestinal tract. This procedure resulted in a prompt hematopoietic effect signaled by a maximum production of 17.1 per cent of reticulocytes on the eighth day of the therapy and an increase of total red blood cells from an initial level of 1.43 to 2.93 million per c.mm. within

eighteen days. This experiment clearly indicated the ability of the essential interaction between beef muscle and gastric juice to take place in a neutral environment and plainly demonstrated the inadequacy of the previous experiments with the normal duodenal contents to decide the point of whether the secretions of the duodenum itself were effective or not in terms of these reactions. The fact that the effective gastric juice here used contained no bile was excellent evidence that the effects previously seen in the numerous experiments with gastric juice were certainly not due to the occasional presence of duodenal contents in small amounts. Although it now appeared that the positive effects observed with the duodenal contents were in all probability due to the presence of an admixture of normal gastric juice, it remained to confirm this and to determine whether normal duodenal contents were not also capable of producing such an effect.

(f) *The Effect of the Incubation of Beef Muscle With Normal Human Duodenal Contents Containing no Gastric Juice (in Neutral Solution).* Accordingly, an apparatus for collecting duodenal contents relatively free from gastric juice was constructed and is described because of its possible use to other investigators. (See illustration.)



Apparatus for collecting separately simultaneous samples of gastric and duodenal contents. *A*, Rehfsuss tube to be placed with tip in duodenum for collection of duodenal contents; *B*, rubber balloon to be distended with 12 per cent sodium iodid solution and placed just proximal to the pylorus; *C*, Rehfsuss tube communicating with interior of balloon; *D*, large tube containing tubes *A* and *C* and remaining in the stomach for collection of gastric juice; *E*, glass cannula for separating lumina of tubes *A*, *C* and *D*.

A rubber tube, *D*, of moderate stiffness 72 cm. long, 8 mm. in external and 6 mm. in internal diameter, was passed over two Rehfsuss tubes, size No. 12 French. One tube, *A*, ending in the usual olive tip, was allowed to protrude 18 cm. beyond the lower end of the large tube *D*, after passing independently through a small pear-shaped rubber balloon *B*, some 5 cm. in length, which when just inflated had a diameter of 3 cm. and could safely

be distended to twice that size. The pear-shaped balloon was attached by its stem end, as it were, close to the end of the large tube, to the second small Rehfuß tube *C*, which thus opened into the interior of the balloon traversed by the first Rehfuß tube *A*. The points of penetration of the balloon by the first Rehfuß tube, carrying on its end the olive, and the point of attachment of the second Rehfuß tube to the balloon were made secure against leakage by the insertion within each tube of an appropriate length of small, carefully fire-polished capillary glass tube 1 cm. in length upon which waxed thread could be appropriately wound to secure the tightness of the joints. The lower end of the large tube, *D*, was perforated for a distance of a few centimeters by a series of holes in order to give it greater flexibility and to provide a means of entrance for liquids, which could thence pass throughout the large tube *D* in the space not occupied by the two contained small Rehfuß tubes *A* and *C*. To the upper end of the large tube was fixed a glass cannula, *E*, having three branches through two of which penetrated respectively the small Rehfuß tubes, *A* and *C*, made water-tight thereto by short rubber tube collars. To the third branch was fitted a short length of flexible rubber tube.

It can be seen from the diagram of this apparatus (see illus.) that three independent tubes could in this way be passed into the stomach of an accommodating subject. The first Rehfuß tube, equipped with the olive, could be observed to pass into the duodenum under the fluoroscope. The deflated balloon could now be allowed to progress to the antrum of the stomach adjacent to the pylorus, and there be dilated to a desirable degree with a 12 per cent aqueous solution of sodium iodid. The large tube, *D*, resting in the stomach could be used to remove gastric secretions and thus help the balloon to eliminate them from the duodenum, from which simultaneously the duodenal secretion was being collected following the introduction of 10 cc. of cream through tube *A*. With a little practice on the part of the subjects and the investigator it was found possible to collect about 75 cc. of duodenal juice in an hour, while often over 150 cc. of gastric juice were simultaneously removed. It thus became evident that without these special precautions a considerable quantity of gastric juice would have entered the duodenum. It was therefore not surprising to find that, in contrast to the duodenal contents previously used, the duodenal juice collected in this particular fashion, showed almost no peptic activity on being made acid. The total daily secretion of this specially collected duodenal juice by one subject, amounting to about 75 cc., was used each day in the experiment now to be described.

Two hundred grams of beef muscle were incubated for 2 hours with 50 cc. of water, 5 gm. of pepsin and sufficient strong hydrochloric acid to give a pH of from 2.5 to 3.5. The resulting liquid was then neutralized to pH 7 with sodium hydroxid and to this was added 75 cc. of the "special" duodenal juice presumably free of gastric contents, which had also previously been brought to pH 7 by the addition of a small amount of sodium hydroxid. After thorough mixing, this material was incubated for two hours and then given each day for ten days in the usual manner to the fasting patient. The result of this procedure carried out during the control period of Case 34 is shown in Table I. During this period, no evidence of clinical improvement resulted, there was some diarrhea, which was controlled by paregoric, and on the eighth day there was a trifling increase of reticulocytes to 4.8 per cent. In the succeeding test

period the procedure was identical except that 75 cc. of gastric juice collected in the usual manner were used instead of the "special" duodenal juice. That is to say, after incubation of the beef muscle with pepsin and hydrochloric acid, the mixture was neutralized to pH 7, incubated with gastric juice also at pH 7 and given at that pH to the patient. Prompt clinical improvement took place, and on the eighth day of this therapy the reticulocytes had risen to 28.4 per cent and the total red blood cells increased during a sixteen-day period from 1.21 to 2.33 million per c.mm. This result clearly indicates that in all probability the normal duodenal secretions free of gastric juice are incapable of producing an effect upon blood formation in pernicious anemia by themselves (see also Case 29, Table II) or by an action upon beef muscle; and that the effects seen in the previous observations with normal duodenal contents (Cases 28 and 32) were undoubtedly due to the presence of gastric juice. The trifling rise of reticulocytes produced by the "special" duodenal contents in the control period of this experiment is scarcely to be taken as evidence of a hematopoietic effect, but if so, is likewise due in all probability to traces of gastric juice entering the duodenum in spite of all precautions. The test period of this experiment, furthermore, amply confirms the observation made in Case 33 that the effective agent in the gastric juice can interact with the beef muscle at a neutral reaction.

The experiments so far reported make it virtually certain by the exclusion of other possible components that the intrinsic factor involved in the production of the hematopoietic substances concerned in these experiments is secreted by the normal human gastric mucosa, and so is present as a constituent of the fasting gastric juice secreted after histamin injection. Furthermore, the fact that the effective interaction of the gastric juice and beef muscle may take place in neutral solution excludes at once the possible rôle of pepsin in this process. In considering other enzymes known to be secreted by the gastric mucosa, particularly those concerned with action on protein, the properties of rennin were reviewed, this enzyme being, after pepsin, perhaps the most clearly defined. Rennin is active in neutral or very weakly acid solution,¹⁴ and has properties of thermolability which may serve to distinguish it from pepsin.¹³ Schmidt-Nielsen,¹⁵ in experiments upon the then disputed question of the identity of rennin and pepsin, found that the neutral milk coagulating power of extracts of calf stomach could be greatly reduced by a temperature of 40 to 42° C. maintained for from one to three days in the presence of hydrochloric acid. It then appeared that such a destructive effect might have been involved in our earlier experiments with pig gastric mucosa and with pepsin. In 1928 we briefly mentioned certain negative experiments on the digestion of beef muscle with pig stomach mucous membrane, using the latter as a potential source of peptic activity after it had been

autolyzed with hydrochloric acid in the incubator.⁹ We had also fed certain pernicious anemia patients 200 or more grams daily of this autolyzed pig gastric mucosa. Those experiments were either entirely negative, like those with pig pepsin^{9,10} now reported in full, or showed a doubtful effect on blood formation. Recently the work of Sturgis and Isaacs¹⁶ and of Sharp¹⁷ now confirmed by Conner¹⁸ and by Wilkinson,¹¹ has demonstrated the effectiveness of the feeding of desiccated preparations of pig stomach in pernicious anemia. An obvious difference between our experiments and those of Sturgis and Isaacs or of Conner is the successful therapeutic use by these investigators of fresh or merely dried stomach tissue. In our experiments with the pig gastric mucosa the tissue was always incubated at 37.5° C. for at least forty-eight hours in the presence of hydrochloric acid. In the preparation of commercial pepsin, a process which lasts several days, a temperature of 44.5° C. is permitted in the presence of acid.⁸ Judging from the work of Schmidt-Nielsen¹⁵ such conditions could reasonably be expected to change certain properties at least of the enzymes of the fresh gastric mucosa capable of acting at the neutral point. For these reasons it was decided to repeat our original experiments with autolyzed pig gastric mucosa incubated with beef muscle using, instead, as a potential source of enzymes, as nearly fresh pig gastric mucosa as possible.

(g) *The Effect of the Incubation of Beef Muscle With Pig Gastric Mucosa.* Fresh pigs' stomachs were obtained at the slaughter house, opened and washed with cold water. The mucosa was then separated from the muscular layer and placed in the icebox. Each day a suitable amount of this tissue was run through a fine meat chopper and 100 gm. of the prepared material mixed with 200 gm. of beef muscle, 4 gm. of pepsin, and enough water to give a semiliquid mass. Strong hydrochloric acid was then added until an acidity of between pH 2.5 and 3.5 was obtained and the mixture incubated for two hours. The material was then removed from the incubator, neutralized to pH 7 with sodium hydroxid, and again incubated for one hour. It was then poured through a fine strainer and given at once to the fasting patient. The data of the control period of Case 36 in Table I show the results of this procedure. An excellent remission was at once forthcoming, with a maximum production of 22 per cent reticulocytes on the eighth day at an initial red blood cell level of 1.72 million per c.mm. This positive result was comparable, according to the data of Minot and his associates,⁶ to the result to be expected from the daily ingestion of about 300 gm. of liver by similar patients and was in contrast to the negative or doubtful results previously obtained under these circumstances with autolyzed mucosa or pepsin incubated with beef muscle. This same patient, Case 36, was now left without medication for a few days since the clinical condition was greatly improved; and when it was observed that the red blood cell count was again diminishing slightly the

observation of the control period was repeated in all its details, except that 25 instead of 100 gm. of the mucosa were incubated with 200 gm. of beef muscle. Again, as is shown by the data in Table I, a production of reticulocytes took place, indicating a positive effect; this time, as was to be expected as a result of the recently preceding positive therapy, the production of reticulocytes attained a maximum of only 8.6 per cent on the eighth day, with an initial count of 1.55 million red blood cells per c.mm. This treatment was discontinued on the eleventh day before an appreciable increase of red blood cells had occurred.

Sturgis and Isaacs¹⁶ first demonstrated the effect of feeding whole, dried pig stomach in pernicious anemia. They state that the daily ingestion in this form of the equivalent of from 190 to 218 gm. of the fresh stomach tissue gave maxima of 18.8, 14.9 and 25.3 per cent of reticulocytes for corresponding initial red blood cell counts respectively of 0.95, 0.73 and 1.47 million per c.mm. These effects are roughly comparable to the result expected from the feeding of similar amounts of liver, since the first two reticulocyte percentages are below, and the last one is above the average figures of about 20, 25 and 15 per cent to be assumed from the data of Minot and his associates.⁶ Since it did not seem probable that the maximal effect in the first period of the experiment just described or the distinct effect seen in the second period could have been caused by the individual action of the small amounts of pig gastric mucosa fed without supposing an interaction with the beef muscle we so stated in a recent preliminary publication.^{18a} Subsequently, however, we have been forced to conclude from the results of other experiments in which definite reticulocyte responses appeared from the daily administration of as little as 30 gm. of fresh mucosa alone that the effects seen in the observations on Case 36 may have been entirely due to the independent action of the gastric mucosa. Since the incubation of this material for forty-eight hours in our original experiments or boiling for five minutes in other experiments rendered it ineffective, it is probable that the properties of this material are not those of liver extract, which is relatively heat resistant. On the other hand, the thermal conditions under which the effectiveness of the fresh mucosa is destroyed are similar to those abolishing the effectiveness of human gastric juice (Case 6¹ and Case 20) and thus suggest the probability of an action of a thermolabile factor in the mucosa upon other constituents of the gastric mucosa much as human gastric juice acts upon beef muscle. Apparently the addition of beef muscle to the fresh mucosa does not ordinarily add to the effect of the action of this factor, although, judging from the decided effects seen in the observations on Case 36, it is possible that such action may have taken place there.

As a result of the experiments so far reported, it may, then, reasonably be concluded that the intrinsic factor involved in the

production of the hematopoietic substance by interaction with beef muscle is undoubtedly secreted by the mucosa of the normal human stomach. On the contrary, it is also apparent that this intrinsic factor is not demonstrably present in normal human saliva or duodenal contents free from secretions of the gastric mucosa; nor has the patient with pernicious anemia been found able to produce the hematopoietic substance from beef muscle ingested as such, unless potentially exposed to the action of the secretions of the normal human stomach proper. Furthermore, it has been shown that this reaction between normal human gastric juice and beef muscle will take place in neutral solution. A similar reaction may apparently be carried out by the fresh mucosa of the pig's stomach, but not by the action of pig pepsin upon beef muscle or by pig stomach mucosa after prolonged incubation with acid.

Analysis of the Nature of the Extrinsic Factor. Since protein-splitting enzymes are considered to be outstanding constituents of gastric juice, it appeared entirely possible that the extrinsic factor of the effective reaction might be protein in nature. The beef muscle acted upon by the gastric juice was composed mainly of protein (22 per cent) and contained only 3 per cent of fat and perhaps 0.3 per cent of carbohydrate; and the effective principle of Cohn, Minot and their associates¹⁹ and of West²⁰ was believed to be a nitrogenous base and hence possibly a derivative of protein. Perhaps, therefore, with an unjustified expectation of success it was decided to try the effect of the action of gastric juice upon the proteins of the beef muscle free from carbohydrate and fat.

(a) *The Effect of the Incubation of Beef Muscle Proteins With Normal Human Gastric Juice.* The preparation of sufficient quantities of protein from beef muscle in as unchanged a state as possible involved some difficulties and resulted in the failure referred to² in the control period of the experiment on Case 24. This failure is believed to have been due to the denaturization of the protein by the incautious addition of strong sodium hydroxid in the original solution of the proteins. A method based upon the precipitation of the muscle proteins, having an isoelectric point in the vicinity of pH 6 was eventually evolved and utilized in the experiments now reported. Two hundred grams of beef muscle were thoroughly mixed with a liter of physiologic salt solution by means of an electric stirrer; and sufficient sodium hydroxid was added to produce a pH of 9.2. The resulting solution was then allowed to stand and the fat skimmed from the surface as completely as possible. The solution was filtered through a fine wire strainer which removed the undissolved connective tissue and then diluted with more physiologic salt solution to a volume of 10 liters in a precipitating jar. After standing a few minutes the small amount of fat remaining on the surface was removed and hydrochloric acid added slowly while the mixture was stirred until a pH of 6 was reached. As this reaction

was approached a copious white precipitate appeared. After sedimentation had taken place, the hemoglobin tinged, supernatant fluid was removed and the precipitate washed twice with 10 liters of salt solution at pH 6. The protein precipitate was now placed upon compress cloth and most of the salt solution expressed. Tests of this material showed no carbohydrate and only traces of fat on ether extraction. The main constituent of the grayish-white precipitate was regarded as in all probability muscle globulin, on account of its characteristic isoelectric point.²¹ All of the protein thus prepared from 200 gm. of beef muscle was used daily in the preparation of the material fed to each patient.

Since it had been shown that both gastric juice and beef muscle were individually ineffective, no control periods were required in these experiments. To each of 4 patients, Cases 25, 26, 27 and 35, were given daily after neutralization to pH 5, the material obtained after the incubation of this protein with 150 cc. of gastric juice for two hours at pH 2.5 to 3.5 in the presence of hydrochloric acid. From the data given for the test periods of these cases in Table II, it may be seen that satisfactory remissions occurred in all of these patients, the average maximum reticulocyte production being very little less than that obtained with the whole beef muscle in otherwise similar experiments. Case 27 was given each day for ten days immediately preceding the test period with beef muscle proteins, a similar period with 100 gm. of wheat gluten flour (44.8 per cent protein) after digestion with 150 cc. of gastric juice daily. No effective substance was formed by this procedure. This patient developed an infection after ten days of the successful test period with beef muscle protein which rendered it undesirable to continue the observation, and liver extract was accordingly begun before a perceptible increase of the total red blood cell count had occurred. Case 35 was also complicated by cystitis and showed subsequently to the twelve days of the test period only a slow increase of red blood cells with liver extract. In Cases 25 and 26 satisfactory total red blood cell increases were obtained with the continuation of the digested beef muscle protein.

In the observations upon a fifth patient, Case 29, a further attempt at purification of the protein was made in order to eliminate, if possible, the last traces of fat. Instead of simply twice washing the precipitate originally formed in the salt solution at pH 6, it was twice redissolved in fresh salt solution at pH 9.2 and reprecipitated at pH 6. In spite of this, traces of ether soluble materials persisted, and the material proved totally ineffective in two ten-day periods of incubation respectively with 150 cc. of normal human duodenal contents and with 150 cc. of gastric juice daily. Since this patient then showed an excellent response to liver extract, it is necessary to suppose this failure of the purified protein to react like the previous preparations as due to a difference in the

method of preparation. It is, of course, possible that some carbohydrate or lipid substance was the basis of the previous positive results, but this seems unlikely since carbohydrate was absent and only traces of ether-soluble material were present in all the protein preparations. More probable is the explanation that the redissolving of the protein at pH 9.2 caused denaturization, or that loss of some essential protein occurred, since some precipitation was observed to occur on either side of pH 6, a value which was empirically selected as the point of approximately maximum precipitation. At any rate, on the basis of the other four positive results it appears reasonable to accept provisionally the idea that in all probability protein or some closely related substance is the extrinsic factor in the reaction between the normal human gastric juice and the beef muscle.

Discussion. The experiments described in the preceding papers of this series^{1,2} made it seem highly probable that the basis of the formation of the substance effective in pernicious anemia, in terms of the hematopoietic reactions described, is the interaction of an intrinsic factor in the normal gastric juice and an extrinsic factor in the beef muscle. The observations recorded here confirm in general those already reported and delineate somewhat the nature of both factors. It can now be said with certainty that the intrinsic factor is a substance secreted by the normal gastric mucosa, since it has been demonstrated that neither normal saliva nor duodenal contents free from gastric juice are able to produce from beef muscle the effective substance, and since gastric juice free from duodenal contents is fully effective. Additional confirmation is added by the demonstration of the capacity of fresh pig gastric mucosa to produce an effective principle of similar hemolability. These observations, furthermore, correlate perfectly, on the one hand, a clearly demonstrated ability of the secretions of the normal gastric mucosa to produce by interaction with beef muscle a substance capable of promptly relieving patients with pernicious anemia of their anemia and, on the other hand, the total inability of these patients, whose outstanding and irremediable defect is a persistent achylia gastrica, to produce in themselves such a substance from beef muscle. The experiments are, then, uniformly in support of our original conception of the nature of the disease Addisonian pernicious anemia as due to a virtual deficiency brought about, even in the presence of a diet adequate for the normal individual, by defective gastric digestion of protein as a result of the achylia gastrica.

The most obvious objection that can be raised to this unqualified position is that many individuals, without clear evidence of pernicious anemia, appear to have a marked inability to secrete hydrochloric acid in the stomach. This is indeed a difficult problem even though the number of such individuals can be materially reduced

by the discrimination possible by modern methods of gastric analysis. By the use of the fractional alcohol meal²² followed by histamin injection³ many of the so-called cases of achlorhydria in individuals without pernicious anemia can be eliminated, but there remain not a few with an achlorhydria which the best methods will not serve to differentiate from the gastric condition found in manifest cases of pernicious anemia. Frequently, however, a critical study of the blood of such individuals shows evidence of abnormal marrow activity even with red blood cell counts and hemoglobin concentrations within normal limits. Some of these individuals have a definite anemia of a secondary or chlorotic type, particularly the members of the families of patients with pernicious anemia^{23,24} and a few such cases have been observed later to develop pernicious anemia.²⁵ It is therefore possible that even with an apparently complete loss of acid secretory power, considerable time is necessary for the elimination of a hypothetic supply of preventive principle from the body. It is even conceivable that small amounts of the effective substance are normally ingested with animal foods other than liver or kidneys,²⁶ particularly since there is now evidence of a possible gradual failure of the absorptive capacity of the intestinal tract for the necessary substance, suggested by the differences in the amounts of liver extract necessary to maintain a normal red blood cell count in different pernicious anemia patients.²⁷

However, to give an answer to the problem, it is only necessary to point out that the present experiments demonstrate that the effective principle can be made by the interaction of normal gastric juice and beef muscle in a neutral environment (Cases 33 and 34), and that the activity in this respect of normal human gastric juice cannot be simulated by the action of pepsin and hydrochloric acid on beef muscle (Cases 9, 10 and 21). With this elimination at one stroke of the relevance of the time-honored essentials of gastric analysis, the hydrochloric acid and the pepsin determinations, no necessarily applicable test remains at the moment for the detection of what kind of gastric juice may contain the essential factor. It is now plainly an unwarranted assumption to suppose that the titration of acidity and the estimation of pepsin are necessarily of value for detecting the essential constituent of effective gastric juice. Although it is probable that the absence of both hydrochloric acid and pepsin from the gastric contents may often indicate also the absence of this other essential, such is certainly not necessarily the case.*

On the other hand, the explanation of the disease on the basis of

* We now have unpublished data showing that the gastric juice of two cases of chronic chlorosis and one of idiopathic achlorhydria with a normal blood, all of which were totally unable to secrete hydrochloric acid, was as effective, after incubation with beef muscle, as normal human gastric juice under those circumstances in bringing about remission in cases of pernicious anemia.

an achylia gastrica may be objected to because occasionally cases with the blood picture of pernicious anemia are reported with an apparently normal gastric function.^{28,29} It is not contended that the mechanism now disclosed by these experiments as the probable basis of cases of pernicious anemia with achylia gastrica is the sole mechanism for producing all instances of the disease. However, it is perhaps highly significant that the commonly alleged causes of pernicious anemia are all potentially related to the function of the gastrointestinal tract. With many of these, indeed, there is a coëxisting achylia, but there may be an apparently normal gastric function, in terms, it is true, of tests which are here shown to be not necessarily discriminative. The belief that abnormality of the gastrointestinal tract in pernicious anemia has a causal relationship to the disease is not new and is, in our opinion, well founded on numerous clinical and certain experimental facts. The clinical evidence that achylia gastrica as produced by hereditary influences, chronic alcoholism, extensive cancer and gastric resection is responsible for certain cases, has already been reviewed^{1,30} and the probable mechanism clearly demonstrated.² Cases of anemia closely simulating the blood picture of pernicious anemia with apparently normal gastric secretions have been reported^{28,29} and encountered in our experience,* but in such instances there have usually been other disturbances of the intestinal tract such as short circuits of the small intestines³¹ or chronic diarrhea.³² Partial obstructions^{33,34} or diseases associated with persistent gastrointestinal tract symptoms such as sprue,^{35,36} pellagra³⁷ or infestation with tapeworm³⁸ or other intestinal parasites³⁹ have been given as causes of pernicious anemia. In most of these cases, however, there was stated to be an absence of free hydrochloric acid from the gastric contents. Seyderhelm⁴⁰ has reported experiments of great interest in which, by producing a stenosis of the small intestine in dogs, in 2 out of 10 animals a blood picture resembling pernicious anemia has been produced.

When interpretations of these different observations have been attempted it has usually been in terms of the action of hypothetic toxins. It now appears possible to explain these apparently divergent causes of a single disease entity on a uniform basis by the logical consequences of the mechanism revealed by our experiments. Since the effective substance has been shown to be formed within the lumen of the normal human stomach, unless it is to be lost to the uses of the organism, it must be absorbed from some part of the gastrointestinal tract. Furthermore, it can now be stated that although the effective mixture of gastric juice and beef muscle

* The gastric juice of two such cases has recently been tested for its ability to produce the effective principle from beef muscle, and although containing normal amounts of hydrochloric acid, pepsin and rennin, was found to be totally ineffective.^{1,9}

appears to have an effect on blood formation identical with that of the material contained in liver when either is given by mouth^{6,7} or when the latter is given by rectum⁴¹ or intravenously,⁴² it has an entirely different thermostability from the principle contained in liver. Now, if it be assumed that the final effective substance, in terms of the hematopoietic reactions, is a single substance, and that substance the one contained in liver, it follows that at some point between the stomach and the bone marrow a conversion of the effective principle created by the presence of beef muscle in the normal stomach into the active principle present in liver must occur. This suggestion is enough to indicate the possibility that any one of a series of defects relating either to the chemistry of the hypothetical conversion process, or certainly to the absorption or distribution within the body of the final effective principle may result in a deficiency of the final effective substance. Next to a defect of the original formative process within the stomach, the loss of the absorptive power of the intestinal tract either mechanically or by bacterial invasion, or the destruction in the bowel of the effective principle after formation would be the most obvious ways in which a deficiency of the final effective substance could be brought about. These remarks indicate that a defect of gastric function alone is not necessarily the only way in which, quite in accord with our hypothesis of the nature of the disease, a deficiency of the necessary substance might be produced.

The experiments reported in this paper add confirmation to the idea that the intrinsic factor of the essential mechanism of the normal stomach for the production of the effective principle resides in the secretions of the normal gastric mucosa itself. That neither normal saliva (Case 23) nor duodenal contents free from gastric contents are effective agents has been clearly shown (Case 34); and that the pernicious anemia patient is totally impotent in this respect has been directly proved¹ (Cases 1, 4 and 10). The present experiments plainly demonstrate, however, that the process is not necessarily due to an enzyme action in an acid medium as was before tentatively suggested by us.^{2,10} That hydrochloric acid alone is not responsible for this reaction has already been amply demonstrated.^{1,2} (Cases 2, 16 and 17.) That an acid hydrolysis by pepsin is not the basis of the observed activity is evidenced by the negative effects of the incubation of beef muscle with pepsin and hydrochloric acid (Cases 9, 10, 21, etc.). Indeed, the supposition that an acid environment is necessary for the essential process is eliminated by the demonstration of the positive effect of normal gastric juice on beef muscle at the neutral point (Cases 33 and 34). That an organic substance in the normal gastric juice is acting upon the beef muscle is suggested by the demonstration that the subsequent hematopoietic reaction is lacking if the gastric juice has been heated to from 70° to 80° C. for a half hour before incubation with the beef muscle.

The problem of the nature of the intrinsic factor, therefore, narrows itself to a consideration of what thermolabile constituent of the secretions of the normal gastric mucosa acting in a neutral environment can be responsible. The preparation of relatively pure proteins from the beef muscle without noteworthy diminution of the usual effects seen in the other cases on incubation of whole beef muscle with gastric juice, suggests that the extrinsic factor of the reaction is a protein or closely related substance, not carbohydrate or fat. This observation agrees with the work of Cohn, Minot and their collaborators,^{19,42} and with that of West,^{20,43} who have independently obtained evidence that the active principle of liver extracts effective in the treatment of pernicious anemia is in all probability a nitrogen-containing substance, possibly a nitrogenous base. Since other functions of the gastric juice are carried out by enzymes, it is perhaps reasonable to continue to regard the essential action as possibly due to an enzyme. The destruction of the activity of the gastric juice by heating to from 70° to 80° C. for a half hour is consistent with that idea,¹⁴ although damage to factors other than enzymes could have been brought about. The two important enzymes, capable of acting on protein, which are secreted by the gastric mucosa itself are pepsin and pararennin, or the rennin of the adult stomach.^{13,14} If by pepsin is understood an enzyme acting optimally in the vicinity of pH 2 and not at less acid ranges than pH 4, this enzyme or its like can be at once excluded from consideration, since it has been shown that the essential reaction may take place in a neutral solution (Cases 33 and 34). On the other hand, adult rennin satisfies this requirement and is destroyed under the conditions abolishing the effectiveness of the human gastric juice,¹⁴ and certainly greatly reduced under the conditions employed in the preparation of commercial pepsin from the gastric mucosa of the pig,^{8,15} shown above to have been incapable of the essential interaction with beef muscle. Since other proteolytic enzymes have also been found in human gastric juice, and since it is possible that the effective substance is not an enzyme, it is impossible to define more exactly at present the nature of this essential and heretofore unrecognized function of the normal human stomach.

The original demonstration^{1,9} that the patient with pernicious anemia even under the most favorable conditions cannot form a hematopoietic substance in detectable amounts from beef muscle has now received ample confirmation. The observations of the control periods of Cases 1, 4 and 10, reported in the first paper; of Cases 13, 15 and 17, reported in the second paper; and of Cases 9,*

* The data on Case 9 are given in the table of the first paper of this series¹ as having no control period because the negative control period with pepsin and hydrochloric acid considerably preceded the effective test period with stomach contents. For convenience in Table I of the present paper the test period is given as immediately following.

10,* 20, 21, 23 and 34 now reported, comprising in all 12 periods of observation, show no significant effects of 200 or more grams of beef muscle either fed as such, or after incubation with hydrochloric acid, with pepsin and hydrochloric acid, with normal saliva or with normal duodenal contents containing no gastric juice. This group of experiments clearly indicates that there is no effective substance present in detectable amounts in beef muscle, and that the patient with pernicious anemia cannot carry out the effective reaction easily demonstrable with the secretions of the normal gastric mucosa. The data already presented indicate that it is improbable that the essential defect in pernicious anemia resides in a dysfunction of the salivary or duodenal secretions, but in the patently defective gastric juice. This agrees with the observations of others¹² and ourselves that the enzyme activity of the duodenal contents of patients with pernicious anemia are essentially normal. The well-known defect of the secretions of the gastric mucosa itself in these patients is thus further brought into prominence and the contrast with the unique and repeatedly demonstrated effectiveness of the secretions of the normal gastric mucosa is emphasized. These facts, we believe, constitute important further confirmation of the original working hypothesis of the nature of the disease set forth in the first paper of this series.¹

It may then be stated as a result of the experiments reported in this series of papers that:

A marked hematopoietic effect associated with general clinical improvement may be observed with regularity in patients with uncomplicated Addisonian pernicious anemia by permitting the absorption from the gastrointestinal tract of such patients of some substance, or substances, generated in vivo or in vitro by an interaction of an intrinsic factor (a) and an extrinsic factor (b). An intrinsic factor (a) secreted by the active normal gastric mucosa, and not present in detectable amounts in the gastrointestinal tract of patients with pernicious anemia or in normal saliva or duodenal contents free of gastric juice. The factor may be characterized as probably organic in nature, destroyed by exposure to a temperature of between 70° and 80° C. for a half hour, or to 44.5° C. for several hours; possibly an enzyme; and active in neutral solution. An extrinsic factor (b) probably protein, or of a closely related nature, obtained by isoelectric precipitation from beef muscle at pH 6.

The evidence from the quantitative action of liver, kidney, and in particular small amounts of potent liver extracts, as has already been pointed out, is clearly in favor of pernicious anemia as a type

* Similarly, the data of Case 10 are given in the table of the first paper of this series¹ as consisting of a negative control period of beef muscle feeding immediately followed by a positive test period with stomach contents. In Table I of the present paper a different negative control period with pepsin and hydrochloric acid is shown, which actually was continuous between the control and test periods of the experiments shown in the table of the first papers of this series.

of deficiency disease.^{1,9,10,44,45} Two or more of its three salient features, gastrointestinal disturbances, neurologic disorders and anemia are found in other diseases now known to be due in part, at least, to a deficiency of the diet, such as pellagra, sprue and beriberi. Our more recent experiments make it appropriate to consider more fully our conception of the disease as due to a virtual deficiency produced not by a defective diet in the usual sense, but by a defect in the patient. It is to be remembered that until food is absorbed from the gastrointestinal tract it is still outside of the body in a functional sense. We believe that our conception of the disease as a deficiency of a new type, brought about indirectly by a defect of the individual which conditions a deficiency not existing for the normal individual, explains the lack of convincing evidence for a direct dietary deficiency. This does not preclude the possibility that abnormal diets may hasten the development of the anemia or have a relationship to the original gastric dysfunction. This conception of the deficiency mechanism has the advantage of simplicity, and now possibly the merit of objective support from our experiments and their recent confirmation by others.^{11,46} It has not been possible to secure palpable results with any of the known vitamins, iron, copper, or even extracts of the liver itself other than certain preparations containing with further purification increasing amounts of nitrogen possibly in the form of a nitrogenous base.^{19,20} Indeed, the conception of the disease as due to a direct deficiency of the food in respect to any of the known vitamins is untenable from numerous observations upon the nature of the effective principle of liver extract already reported by Cohn, Minot and their associates,¹⁹ and particularly in the face of the experiments reported in the second paper of this series.² Therein it was shown (Cases 13, 15 and 17) that certain amounts of beef muscle and normal human gastric juice, if given without opportunity for contact, were ineffective in producing the remissions at once forthcoming if the same amounts of the identical substances were given a chance for interaction. It is difficult to see even a reasonable analogy to the occasional spontaneous recovery of certain animals fed diets deficient in vitamin B, since it is probable that this phenomenon, known as "refection," is due to the fact that bacterial action within the gastrointestinal tract is able to synthesize under certain special conditions the vitamin lacking in the diet.⁴⁷ If the remission in these patients is the response to a "vitamin," it must then be assumed that its synthesis has taken place by an interaction between beef muscle protein and normal human gastric juice.

The facts demonstrated by our experiments present, in our opinion, without invoking the aid of other hypothetic factors, a working concept of the mechanism of pernicious anemia. The peculiar nature of the bone-marrow pathology in relapse⁴⁸ and its highly specific response to particular extracts of liver or to the

products of specific reactions between beef muscle proteins and normal human gastric juice are far more comprehensible as a response to the supplying of a particular deficient substance than as due to the neutralization of "toxins" of so far undemonstrated existence. As Whipple⁴⁹ has pointed out, the arguments for the presence of a toxin are quite as good when used as evidence for a deficiency. The possibility of microorganisms within the gastrointestinal tract acting as a source of toxins⁵⁰ capable of damaging the bone-marrow or destroying the blood corpuscles⁵¹ has been practically eliminated in the opinion of Davidson⁵² by more critical studies of the bacteriology before and after liver therapy. To the clinician familiar at first hand with the quantitative nature of the response of pernicious anemia patients to the administration of a few grams of material constituting adequate liver extract therapy there is something wholly unsatisfactory in conceptions of the etiology of the disease involving toxins.

It is therefore not surprising that since the original demonstration of the effectiveness of liver therapy in pernicious anemia by Minot and Murphy⁵³ has been so amply confirmed, the idea has arisen that a defect of the human liver,^{54,55} or of some organ of the human body analogous to those of the normal animal known to be effective when fed by mouth, might be directly responsible for the development of the disease. Unfortunately, this attractively simple conception does not correlate well with constant, recognizable pathology in the patient except in the case of the dysfunction of the stomach. Also, it is not easy to see why the liver, the kidney^{53,56} and possibly other organs should apparently compete as primary sites of formation of the effective substance unless possibly they are merely storage depots for material formed elsewhere in the normal animal. More logical interest attaches to the recent observations of Sturgis and Isaacs,¹⁶ Sharp,¹⁷ Conner¹⁸ and Wilkinson,¹¹ who have reported marked hematopoietic effects with pig stomach feeding or with extracts of that organ. Sturgis and Isaacs suggest that their experiments give evidence in support of our own, but state that they are at present uncertain whether the effective principle involved is merely present in the stomach of these animals as it is in the liver or kidney or whether it is formed therein by normal physiologic processes or postmortem autolysis. The last possibility was the one originally investigated by us in 1928 with negative results, using pig-stomach mucosa after incubation at 37.5° C. for forty-eight hours in hydrochloric acid.⁹ We have now been able by the administration of 25 or 100 gm. of fresh pig gastric mucosa with or without beef muscle to reproduce the activity of human gastric juice and beef muscle. Since, in contrast to the relative thermostability of liver or liver extract, we have found that boiling for five minutes or incubation in acid for forty-eight hours will destroy completely the effectiveness of pigs' gastric mucosa or of human gastric juice,

we consider that the mechanism of the action of the whole stomach tissue, demonstrated by Sturgis and his associates, is in all probability identical with that involved in our earlier experiments with human gastric juice and beef muscle.

It is perhaps unnecessary to point out, furthermore, that the effectiveness of the whole pig stomach or mucosa after the death of the animal does not necessarily imply the existence of a physiologic process within the gastric tissue itself resulting in the production of similar effects during life, since it involves an artificial set of conditions which do not exist in the case of the physiologic action of normal human gastric juice upon ingested beef muscle in the lumen of the stomach.¹ This distinction between an action of the stomach alone and an action upon its contents is inherent in the hypothesis of the disease which we have advanced, and was expounded in presenting the great significance, for the interpretation of our experiments, of the question of whether the gastric juice of the normal individual was itself effective or only after an interaction with beef muscle.² The classical riddle of gastric physiology as to why the stomach does not digest itself (to form "liver extract") might again become perplexing were it necessary to assume that the mechanism for the formation of the substance responsible for the effects seen in the studies with pig stomach was not merely a simulation postmortem of the physiologic action of the secretions of the normal stomach on its contents during life.

As always, however, in science, the "explanation" explains nothing in a final sense; but it may serve to indicate a profitable direction for further searching. For this reason we have pointed out before¹⁰ a possible analogy between diabetes mellitus and pernicious anemia. Fortunately, through the pioneer work of Banting and Best and of Minot and Murphy, an effective means of control of both diseases has been discovered. The analogy rests also upon the fact, that if our observations and conclusion are confirmed by others, a defective function of one organ of the body will have again been shown to be the basis of a remote or general disturbance. In the case of diabetes the faulty organ is known to be the pancreas; in Addisonian pernicious anemia it is probably the stomach. In diabetes, the internal metabolism of the carbohydrate and fat are disturbed; in pernicious anemia we have tried to show that some step is missing in the manipulation of proteins, external to the body in the biologic sense, although within the gastrointestinal tract. We point out as a final aspect of this analogy, in the hope that it may serve as a directive stimulus to further work, that except for a few special and obvious causes, the nature of the pathologic processes leading to the all-important dysfunction of the islands of Langerhans in the one disease and of the gastric mucosa in the other are as yet unknown.

Summary and Conclusions. 1. The validity of the hypothesis that the genesis of the disease pernicious anemia is dependent upon an inadequate gastric digestion of protein, thus permitting the development of a virtual deficiency in the presence of a diet adequate for the normal individual has been further examined and the nature of the postulated gastric defect somewhat defined.

2. The results of the following observations on cases of Addisonian pernicious anemia are considered to confirm and further characterize those reported in the previous two papers of this series^{1,2} therein stated to be consistent with the above hypothesis.

(a) To one patient was given daily for eight days, without effect on blood formation, the material resulting from the incubation of 200 gm. of beef muscle with normal human saliva.

(b) To another patient was given daily for ten days, without significant effect on blood formation, the material resulting from the incubation of 200 gm. of beef muscle at pH 7 with 75 cc. of normal human duodenal contents, obtained in such a manner as to contain a minimum of gastric secretion. In each of two other patients similarly treated with beef muscle incubated with normal duodenal contents at pH 7 known to contain gastric secretion, a distinct effect on blood formation was obtained similar to that previously observed with beef muscle and normal gastric contents.

(c) To each of three patients was given daily for a period of at least ten days, without effect on blood formation, the material resulting from the incubation of 200 gm. of beef muscle with from 2 to 5 gm. of commercial pepsin (pig) and hydrochloric acid at pH 2.5 to 3.5, for from two to twenty-four hours before neutralization and administration to these patients at pH 5.

(d) To another patient was given daily for ten days, without effect on blood formation, the material resulting from the incubation of 200 gm. of beef muscle with 150 cc. of fasting normal human gastric contents (secreted after histamin stimulation) which had been previously heated to a temperature of from 70° C. to 80° C. for a half hour.

(e) To each of four patients was given daily during test periods of at least ten days the material resulting from the incubation of 200 gm. of beef muscle for two hours with from 75 to 150 cc. of fasting normal human gastric contents secreted after histamin stimulation. In 2 patients the incubation was conducted as usual in the presence of hydrochloric acid at pH 2.5 to 3.5 with subsequent administration to the patient at pH 5; in the other 2 patients both incubation and administration were carried out at pH 7. In the experiments performed with incubation at pH 7 the normal fasting gastric contents used were collected in such a way as to contain no duodenal contents. In all of these patients a marked and progressive effect on blood formation was observed to take place within ten days.

(f) In two periods of observation on one patient 100 and 25 gm. respectively of fresh pig stomach mucous membrane were incubated with 200 gm. of beef muscle, and the resulting material administered daily for two periods of at least ten days each, in both instances with a marked effect on blood formation. Subsequent experiments have indicated the probable independent action of the pig gastric mucosa in these observations.

(g) To each of 5 patients was given daily for at least ten days the material resulting from the incubation of 150 cc. of normal human fasting gastric contents with the washed proteins precipitable at pH 6 from 200 gm. of beef muscle previously dissolved in salt solution at pH 9.2. In all but one of these patients a marked effect upon blood formation appeared within ten days as indicated by characteristic increases of reticulocytes progressing to maxima not significantly less than those obtained in similar experiments with whole beef muscle incubated with gastric contents. In one patient no effect on blood formation occurred.

3. From a consideration of the above experiments and of those of the two preceding papers of this series, the following conclusions were drawn:

(a) The active constituent (Intrinsic factor) of the normal human fasting gastric contents is in all probability secreted by the mucosa of the stomach and is not detectably present in normal saliva or duodenal contents free of gastric juice, or in the secretions of any portion of the gastrointestinal tract of the pernicious anemia patient.

(b) This substance is probably organic, thermolabile, possibly an enzyme, capable of interaction with protein (Extrinsic factor) or closely related substances in neutral solution, resulting in the production of material having, when administered to pernicious anemia patients, a marked hematopoietic effect. If an enzyme, it is certainly not pepsin; its properties as so far determined are only in certain respects similar to those of rennin.

(c) The lack of this particular property (Intrinsic factor) of the gastric contents in pernicious anemia is probably the essential defect leading to the development of the disease, through a failure of the normal reaction, occurring in these experiments with beef muscle proteins, (Extrinsic factor) and normal human gastric juice.

4. It is also concluded that the existing tests for hydrochloric acid and pepsin of the gastric juice are not necessarily of value in determining the presence or absence of the intrinsic factor essential to the reactions between normal human gastric juice and beef muscle described in these papers.

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BIBLIOGRAPHY.

1. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, *Am. J. Med. Sci.*, 1929, 178, 748.
2. Castle, W. B., and Townsend, W. C.: Ibid. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation With Normal Human Gastric Juice, *Am. J. Med. Sci.*, 1929, 178, 764.
3. Gompertz, L. M., and Vorhaus, M. G.: Studies on the Action of Histamin on Human Gastric Secretion, *J. Lab. and Clin. Med.*, 1925, 11, 14.
4. Levine, S. A., and Ladd, W. S.: Pernicious Anemia: A Clinical Study of One Hundred and Fifty Consecutive Cases with Special Reference to Gastric Anacidity, *Bull. Johns Hopkins Hosp.*, 1921, 32, 254.
5. Teschendorf, H. J.: Zur Differenzierung der Achylien durch fraktionierte Magenausheberung nach Histamininjektion unter gleichzeitiger Untersuchung des Harnpepsins, *Deutsch. Arch. f. klin. Med.*, 1927, 155, 43.
6. Minot, G. R., Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy: Particularly in Pernicious Anemia, *Am. J. Med. Sci.*, 1928, 175, 581.
7. Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract: Effects Upon the Production of Immature and Mature Red Blood Cells, *Ibid.*, 1928, 175, 599.
8. Wood, H. C., and LaWall, C. H.: The Dispensatory of the United States of America, 21st ed., Philadelphia, J. B. Lippincott Company, 1921, p. 821.
9. Castle, W. B., and Loekke, E. A.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *J. Clin. Invest.*, 1928, 6, 2.
10. Castle, W. B.: The Etiological Relationship of Achylia Gastrica to Pernicious Anemia, *Proc. Roy. Soc. Med.*, 1929, 22, 58; *Ibid.*, Achlorhydria and Pernicious Anemia, *British Med. J.*, 1929, i, 1120.
11. Wilkinson, J. F.: Pernicious Anemia, *British Med. J.*, 1930, i, 236.
12. McClure, C. W., Montague, O. C., and Mortimer, E.: Pancreatic Function in the Absence of Hydrochloric Acid from the Stomach, *Boston Med. and Surg. J.*, 1924, 190, 357.
13. Mathews, A. P.: *Physiological Chemistry*, 3d ed., New York, William Wood & Co., 1921.
14. Waksman, S. A., and Davison, W. C.: *Enzymes*, Baltimore, Williams & Wilkins Company, 1926.
15. Schmidt-Nielsen, S.: Über die vermeintliche Identität von Pepsin und Chymosin, *Ztschr. f. physiol. Chem.*, 1906, 48, 92.
16. Sturgis, C. C., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, *J. Am. Med. Assn.*, 1929, 93, 747.
17. Sharp, E. C.: An Antianemic Factor in Desiccated Stomach, *J. Am. Med. Assn.*, 1929, 93, 749.
18. Conner, H. M.: The Treatment of Pernicious Anemia with Swine Stomach, *J. Am. Med. Assn.*, 1930, 94, 388.
- 18a. Castle, W. B., Townsend, W. C., and Heath, C. W.: Further Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia. *Proc. Meet. Am. Soc. Clin. Invest.*, May 5, 1930, in press. *J. Clin. Invest. Lancet*, 1930, 218, 1062.
19. Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia, II., *J. Biol. Chem.*, 1928, 77, 325.
20. West, R., and Nichols, E. G.: Liver Fractions in Pernicious Anemia, *J. Clin. Invest.*, 1928, 6, 3.
21. Salter, W. T.: Certain Physico-chemical Characteristics of Muscle Globulin, *Proc. Soc. Exp. Biol. and Med.*, 1926, 24, 116.
22. Keefer, C. S., and Bloomfield, A. L.: The Significance of Gastric Anacidity, *Bull. Johns Hopkins Hosp.*, 1926, 39, 304.
23. Faber, K., and Gram, H. C.: The Association of Achylia and Anemia of Different Types in Three Members of the Same Family, and the Behavior of the Color Index in Pernicious Anemia, *Arch. Int. Med.*, 1924, 34, 827.
24. Faber, K., and Gram, H. C.: Relations Between Gastric Achylia and Simple and Pernicious Anemia, *Arch. Int. Med.*, 1924, 34, 658.

25. Gram, H. C.: Undersøgelser over den perniciøse anaemis udvikling paa en familie med. talrige tilfaede (Meddelelse fra praxis), Ugeskrift for Laeger, 1929, **91**, 1135.
26. Elders, C.: Tropical Sprue and Pernicious Anemia, *Lancet*, 1925, **i**, 75.
27. Minot, G. R.: Some Fundamental Clinical Aspects of Deficiencies, *Ann. Int. Med.*, 1929, **3**, 216.
28. Grinker, R. R.: Pernicious Anemie, Achylia Gastrica and Combined Cord Degeneration and Their Relationship, *Arch. Int. Med.*, 1926, **38**, 292.
29. Munford, S. A.: Atypical Anemias, *Clifton Med. Bull.*, 1925, **11**, 139.
30. Cornell, B. S.: The Etiology of Pernicious Anemia, *Medicine*, 1927, **6**, 387.
31. Little, W. D., Zerfas, L. G., and Trusler, H. M.: Chronic Obstruction of the Small Bowel, *J. Am. Med. Assn.*, 1929, **93**, 1290.
32. Richardson, W., and Klumpp, T. G.: Sprue: Report of a Case Treated with the Authorized Liver Extract Effective in Pernicious Anemia, *New England J. Med.*, 1928, **199**, 215.
33. Faber, K.: Perniciøse Anämie bei Dünndarmstricturen, *Berl. klin. Wehnschr.*, 1897, **34**, 643.
34. Meulengracht, E.: Pernicious Anemia in Intestinal Stricture, *Acta med. scand.*, 1929, **72**, 231.
35. Wood, E. J.: Pernicious Anemia in Its Relationship to Sprue, *Am. J. Med. Sci.*, 1925, **169**, 28.
36. Baumgartner, E. A., and Smith, G. D.: Pernicious Anemia and Tropical Sprue, *Arch. Int. Med.*, 1927, **40**, 203.
37. Mollow, W., and Klein, B.: Beiträge zur Klinik der Pellagra, *Arb. ü. Tropenkrankh.*, 1927, **p. 349**.
38. Isaacs, R., Sturgis, C. C., and Smith, M.: Tapeworm Anemia, *Arch. Int. Med.*, 1928, **42**, 313.
39. Logan, A. H.: Balantidium Coli and Pernicious Anemia: Report of Four Cases, *Am. J. Med. Sci.*, 1921, **162**, 668.
40. Seyderhelm, R., Lehmann, W., and Wichels, P.: Experimentelle intestinale perniziöse Anämie beim Hund, *Klin. Wehnschr.*, 1924, **3**, 1439.
41. Reznikoff, P.: Rectal Administration of Liver Extract (Cod), *J. Am. Med. Assn.*, 1929, **93**, 367.
42. Cohn, E. J., McMeekin, T. L., and Minot, G. R.: The Nature of the Material Effective in Pernicious Anemia, III, *Am. J. Physiol.*, 1929, **90**, 316.
43. West, R., and Howe, M.: Liver Fractions in Pernicious Anemia, *J. Clin. Inves.*, 1929, **1**, 495.
44. Means, J. H., and Richardson, W.: Impressions of Nature of Pernicious Anemia in Light of the Newer Knowledge, *J. Am. Med. Assn.*, 1928, **91**, 923.
45. West, R.: Pernicious Anemia as a Deficiency Disease, *Ann. Int. Med.*, 1929, **3**, 132.
46. Ungley, C. C.: The Stomach and Pernicious Anemia, *Newcastle Med. J.*, October, 1929.
47. Fridericia, L. S., Freudenthal, P., Gudjonsson, S., Johansen, G., and Schoubye, N.: Refection, a Transmissible Change in the Intestinal Content, Enabling Rats to Grow and Thrive Without Vitamin B in the Food, *J. Hyg.*, 1927, **27**, 70.
48. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, *Am. J. Pathol.*, 1927, **3**, 179.
49. Whipple, G. H.: Hemoglobin Construction Within the Body as Influenced by Diet Factors, *Am. J. Med. Sci.*, 1928, **175**, 721.
50. Hurst, A. F., and Bell, J. R.: The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord with Special Reference to Its Connection with Addison's (Pernicious) Anemia, Achlorhydria, and Intestinal Infection, *Brain*, 1922, **45**, 266.
51. Seyderhelm, R.: Die Lebertherapie der perniziösen Anämie, *Ergeb. d. ges. Med.*, 1929, **13**, 521.
52. Davidson, S.: The Ætiology of Pernicious Anemia: A Review of the Factors Concerned in Its Production, *Edinburgh Med. J.*, 1928, **35**, 322.
53. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, *J. Am. Med. Assn.*, 1926, **87**, 470.
54. Harris, S.: Etiology of Pernicious Anemia: Is It Secondary to Hepatic Infection, Resulting in Deficiency of Liver Endocrine? *Internat. Clin.*, 1928, **2**, 120.
55. Schwarz, E.: Megaloblastisches Blutbild und Leber, *Wien. klin. Wehnschr.*, 1928, **41**, 192.
56. McCann, W. S.: Effect of Kidney on Blood Regeneration in Pernicious Anemia, *Proc. Soc. Exp. Biol. and Med.*, 1928, **25**, 255.

THE NORMAL FILAMENT AND NONFILAMENT POLYMORPHO- NUCLEAR NEUTROPHIL COUNT: ITS PRACTICAL VALUE AS A DIAGNOSTIC AID.

BY DAVID L. FARLEY, M.D., HUSTON ST. CLAIR, M.D.,

AND

JOHN A. REISINGER, M.D.,

PHILADELPHIA, PA.

(From Medical Service A, Pennsylvania Hospital, Philadelphia, Pa., and the Cooper Hospital, Camden, N. J.)

IN 1904, Arneth brought forward his classification of the neutrophilic leukocytes. He separated them into five classes, according to the number of nuclear lobes of the cell. Those with a slightly indented or band-shaped nucleus were placed in Class 1, those with two lobulations in Class 2, those with three lobulations in Class 3, and so on. He determined that the occurrence of these cells in a normal individual was as follows:

Class 1	5 per cent
Class 2	35 per cent
Class 3	41 per cent
Class 4	17 per cent
Class 5	2 per cent

He thought that as a polymorphonuclear neutrophil increased in age and differentiation, the number of lobulations increased from Class 1 upward to or beyond Class 5. He believed that a cell of three nuclear lobes was an older and a more differentiated cell than one with a single lobulation. An acute infection with leukocytosis caused a "shift to the left," that is, a higher percentage of cells were found in the groups toward the left of the written page. Subsequent experimentation served to substantiate most of Arneth's conclusions in regard to his index of the polymorphonuclear cells, especially the important fact of "the shift to the left" in the presence of stimulation of the myeloid tissue by infection. The Arneth count, however, has fallen into disuse because of its complexity and the labor required in estimating the different classes.

Schilling (1920) devised a simpler index. He divided the granular neutrophilic leukocytes into four classes, viz., with simple round nucleus (myelocyte), with slightly indented nucleus (young form of metamyelocyte), with deeply indented nucleus (band form of metamyelocyte), and with segmented nucleus. He established that an average of about 4 per cent of the total leukocytes are band forms. Schilling and others have considered serial differential counts with consideration of the quantitative changes of neutrophils (nuclear shift) of far more importance than the total leukocyte count. Pons and Krumbhaar (1924) suggested that all essentials for clinical

purposes would be served if all neutrophils were divided into three classes: (1) metamyelocytes (very young)—with round or slightly indented nuclei; (2) nonsegmented forms (young)—when the nuclear material was connected by broad bands; (3) segmented forms (older)—when two or more groups of nuclear material were joined by narrow filaments. Piney (1928) would disregard in the routine count Schilling's Class 1 and 2 (myelocytes and young forms of metamyelocytes), since they appear so seldom in infection as to be of little clinical significance.

Cooke and Ponder (1927) also were of the opinion that it was impossible to arrive at constant results by Arneth's method and they evolved a method, termed the polymorphonuclear count. This is a simpler classification than that of Arneth. The polymorphonuclear neutrophil with an undivided nucleus is placed in their Class 1; in Class 2 is placed the cell whose nucleus has divided into two lobes; in Class 3 the cell with three lobes; and so on to Class 5. They state that the difficulty lies in determining whether or not the nucleus has divided; that the polymorphonuclear nucleus never divides completely; that there is always a fine filament of nuclear material uniting the different lobes. Therefore, as the basis of differentiating the five classes, Cooke's criterion is as follows: "If there is any band of nuclear material except this chromatin filament connecting the different parts of a nucleus, that nucleus cannot, for the purposes of the count, be said to be divided." They illustrate diagrammatically (see Fig. 1). The different groups of Cooke and Ponder are made plain by Fig. 2.

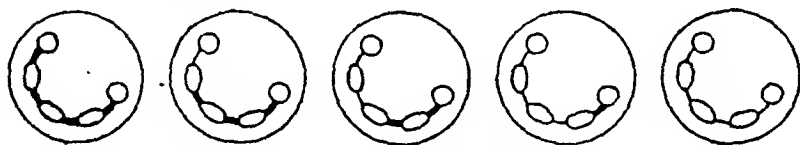


FIG. 1.—Scheme of Cooke and Ponder, illustrating Cooke's criterion. "If there is any band of nuclear material except a fine filament of nuclear material connecting the different parts of a nucleus, that nucleus for the purposes of the count cannot be said to be divided." (From "The Polynuclear Count," by Cooke and Ponder, London, Charles Griffin & Co., 42 Drury Lane, 1927.)

AUTHORS' WORK. The classification of the different types of polymorphonuclear neutrophils which we have attempted, is based upon the work of Arneth, Schilling, Piney, Pons and Krumbhaar, and more directly upon that of Cooke and Ponder. It appears that the differential estimation of the variations in the appearance of the nuclei of the neutrophils is a more delicate indication of infection than the ordinary total and differential count. Our attempt is to popularize a valuable method by further simplification, thus making it available for those lacking special training in blood examinations. It is our feeling that whenever and wherever a differential leukocyte count is made, the percentage of the different types of polymorphonuclear leukocytes should be determined.

In reviewing the work of Arneth, Schilling, and Cooke and Ponder, it seems that the classification of Arneth is too complicated for ordinary use, and that the method of Schilling lacks the clear-cut differentiation of cell nuclei which can be attained by following Cooke's criterion. The valuable classification of Cooke and Ponder can be simplified for the ordinary worker by dividing their five

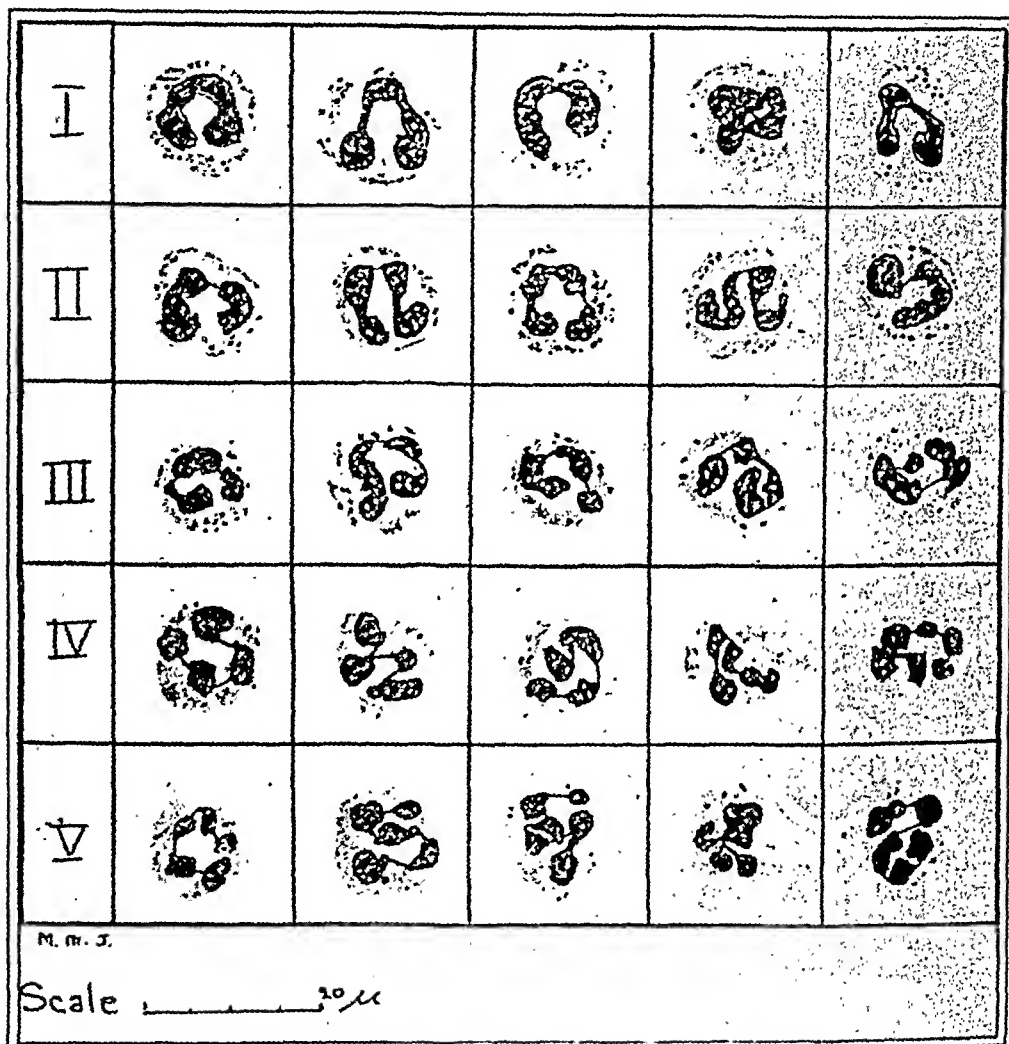


FIG. 2.—The five classes in the polynuclear count of Cooke and Ponder. If there is any band of nuclear tissue except a chromatin filament, uniting the nuclear masses, those parts must not be considered as separate segments. (From "The Polynuclear Count," by Cooke and Ponder, London, Charles Griffin & Co., 42 Drury Lane, 1927.)

classes into two classes, the first class to be identical with their Class 1, and the second class to include their Classes 2, 3, 4 and 5. Cooke's criterion serves for our purposes, thus to divide the polymorphonuclear neutrophils into two classes, "nonfilament" neutrophils and "filament" neutrophils. Distinct myelocytes or myeloblasts are to be counted as such. This is similar to the method of

Pons and Krumbhaar, except that their infrequent group of the metamyelocyte is here included in the nonfilament form. Cooke and Ponder have shown that the percentage of error in their classification when 50 neutrophils are counted is $+0.09$ and a satisfactory count can be obtained when as few as 50 cells are counted. We have adopted, therefore, the ordinary differential count where 100 cells are counted, as the basis of our work. Stated in simple terms, our count is the differentiation of 100 consecutive leukocytes to determine the percentage of nonfilament neutrophils, filament neutrophils, lymphocytes, monocytes, eosinophils and basophils, in which differential count, Cooke's criterion is used to separate the polymorphonuclear neutrophils into two groups. On this basis, we have attempted to establish a normal nonfilament and filament count in two ways: (1) By mathematics we have reduced the excellent normal chart of Cooke and Ponder; (2) by an actual series of counts on 100 normal individuals, we have attempted to find out especially the upper limit of the normal nonfilament count as well as the average nonfilament count. The upper limit of a normal is sometimes of more practical value than an average.

Reduction of the Normal Counts of Cooke and Ponder. Cooke and Ponder determined the normal polymorphonuclear neutrophil count in man and the extent to which it varied in health by taking the counts for ninety normal persons, each of whom was examined carefully to exclude infection. Their figures are based on counts of 100 neutrophils. By taking 70 per cent of the figures for Class 1, we have reduced their counts to the basis of 70, the usually accepted high normal neutrophil count in an ordinary differential leukocyte count where a total of 100 cells are counted, including leukocytes of all types. Their figures then become:

TABLE I.—TRANSFORMED NORMAL COUNTS OF COOKE AND PONDER.

No.	Non-filament (%)	No.	Non-filament (%)	No.	Non-filament (%)	No.	Non-filament (%)	No.	Non-filament (%)	No.	Non-filament (%)
1	7	16	6	31	9	46	5	61	7	76	6
2	9	17	11	32	9	47	4	62	4	77	9
3	11	18	10	33	7	48	6	63	6	78	5
4	6	19	13	34	7	49	7	64	8	79	5
5	8	20	11	35	5	50	7	65	3	80	7
6	5	21	11	36	5	51	4	66	5	81	4
7	9	22	5	37	7	52	11	67	8	82	5
8	5	23	9	38	2	53	6	68	6	83	2
9	6	24	5	39	9	54	5	69	7	84	7
10	5	25	9	40	8	55	8	70	8	85	4
11	12	26	5	41	7	56	8	71	6	86	7
12	4	27	9	42	5	57	7	72	7	87	5
13	12	28	11	43	4	58	8	73	5	88	8
14	10	29	3	44	3	59	5	74	5	89	8
15	3	30	12	45	5	60	7	75	5	90	4

The average count in 90 individuals is 6.08 cells.

Authors' Normal Counts. *Technique.* After comparing a number of special stains with the ordinary Wright's modification of the Romanowsky stain, we are convinced that excellent results can be obtained with the Wright stain and have used it throughout in our work because of its universal popularity. It is to be emphasized, however, that cover-slip preparations are to be used. We have found blood smears upon the ordinary microscopic slide unsuitable for accurate differentiation between filament and nonfilament neutrophils. The smears must be thin in order to have clear distinction of the nucleus. Thick smears make accurate differentiation impossible. We have taken the counts of 100 normal adults as follows:

TABLE II.—AUTHORS' NORMALS (100 CASES).

No.	Non-fila- ment (%).	No.	Non-fila- ment (%).	No.	Non-fila- ment (%).	No.	Non-fila- ment (%).	No.	Non-fila- ment (%).
1	14	21	12	41	7	61	6	81	8
2	10	22	14	42	7	62	4	82	9
3	11	23	13	43	9	63	5	83	10
4	5	24	9	44	5	64	4	84	6
5	9	25	9	45	12	65	5	85	6
6	14	26	12	46	13	66	3	86	14
7	15	27	10	47	9	67	16	87	9
8	12	28	12	48	3	68	8	88	16
9	13	29	10	49	6	69	6	89	14
10	16	30	7	50	13	70	7	90	12
11	10	31	13	51	13	71	3	91	12
12	11	32	6	52	5	72	12	92	14
13	5	33	11	53	4	73	9	93	10
14	5	34	9	54	8	74	7	94	7
15	13	35	8	55	10	75	8	95	12
16	14	36	14	56	15	76	7	96	8
17	13	37	9	57	8	77	11	97	6
18	10	38	6	58	7	78	6	98	7
19	10	39	7	59	5	79	8	99	11
20	9	40	8	60	3	80	8	100	6

The average count in 100 individuals is 9.2 cells.

The test of a given clinical procedure is often the ease of its application divided by its usefulness. There seems little doubt that the estimation of the young forms of polymorphonuclear leukocytes gives valuable information. It is surprising how universally this conclusion is reached by practically all who have worked in this field. There seems to be, however, no easy method of making such a count and when one attempts to find normal standards, difficulties arise. We have attempted to find out the average normal young polymorphonuclear count (nonfilament forms) and especially the upper limit of the normal count. From our work we believe that 16 per cent can be used to practical advantage as the upper limit in health of normal young polymorphonuclear leukocytes (non-

filament forms) counted as outlined in this article. It is understood, of course, that this figure is somewhat arbitrary, but we have found such a definite figure of considerable practical value. For example, it often becomes necessary to decide whether a patient is merely neurotic and suffering from psychic, anxiety, or exhaustion pains, or whether there is in fact a hidden focus of disease. In such a case, if the young polymorphonuclear leukocytes number more than 16 per cent, we may become more assiduous in searching for the cryptic infection. Negative results, that is, a figure less than 16 per cent, we believe should be regarded as suggestive but not conclusive that the patient has no infection.

The method suggested is not intended to take the place of the more elaborate methods of Cooke and Ponder, Arneth, and others, but is designed especially for routine use. The great majority of blood counts are made by hospital resident physicians. It will be found to entail practically no additional labor in the ordinary differential count if the filament and nonfilament forms of polymorphonuclear neutrophils are estimated. We have found, indeed, that when once such a method is taught to an individual, his curiosity impels him to make such a division of the polymorphonuclears.

Cryptic infections, and cases where the patient may or may not be sick, appear to be the instances where the count is of most value. It would seem that except in unusual instances, the count is of no more value in prognosis than is the degree of temperature reaction. It indicates that the bone-marrow is active or inactive. A trivial infection may cause a marked reaction and *vice versa*. It is interesting to see the great increase in young forms in some cases where there is no hint of abnormality in the ordinary total and differential count. This is seen in those cases of overwhelming infection with normal counts or leukopenia. Patients with lobar pneumonia may have 60 per cent or more young forms without leukocytosis, a hidden picture, unless a young polymorphonuclear leukocyte count be made.

In Table III, we have itemized a few cases where the total and differential count gave an inadequate conception of the bone marrow activity, but where the nonfilament count indicated infection. This was especially noticeable in the cases of chronic pelvic inflammatory disease where usually the temperature also was normal. We compared a number of such cases with simultaneous sedimentation of red-cell estimation. The method of filament and nonfilament counting compared favorably with the sedimentation test. No elaborate comparison was made, but our general impression was that when the sedimentation test was abnormal there was usually an increase in the percentage of nonfilament forms above 16 per cent. These cases were checked by sections made from material removed at subsequent operation.

TABLE III.

	Total white blood cells.	Non- filament poly- morpho- nuclears.	Filament poly- morpho- nuclears.	Lymph- ocytes.	Mono- cytes.	Eosino- phils.	Baso- phils.
1. Pelvic phlebitis	6,200	50	38	2	8	0	0*
2. Pulmonary tuberculosis	6,000	21	42	15	21	1	0
3. Maxillary sinusitis	10,200	22	44	19	13	2	0
4. Acute mastoiditis	7,600	22	55	13	10	0	0
5. Lobar pneumonia	6,800	64	27	5	4	0	0*
6. Pulmonary tuberculosis	7,600	32	47	1	18	2	0
7. Acute sinusitis	9,100	34	37	11	18	0	0
8. Lobar pneumonia	8,700	54	27	12	5	2	0*
9. Subacute hepatitis	10,200	22	31	35	7	4	1
10. Rheumatic fever	9,000	24	35	23	14	1	1
11. Phlebitis	10,200	21	35	26	18	1	0
12. Miliary tuberculosis	8,000	43	25	14	14	2	2*
13. Vincent's angina	7,900	26	26	23	18	0	0
14. Chronic salpingitis	9,900	22	34	33	8	3	0
15. Chronic salpingitis	8,800	25	68	5	2	0	0
16. Chronic salpingitis	6,100	22	54	15	9	0	0
17. Chronic salpingitis	6,900	18	43	26	13	0	0
18. Chronic appendicitis	10,100	28	53	13	6	0	0
19. Chronic salpingitis	10,000	22	54	12	11	0	1
20. Chronic salpingitis	9,300	38	46	15	0	1	0
21. Chronic salpingitis	8,100	25	35	29	10	1	0
22. Abscessed tooth	7,800	28	36	28	6	2	0

* Death.

We have also (Table IV), calculated to our method a group of cases published by Cooke and Ponder.

TABLE IV.

Cooke and Ponder's grouping of counts in infective states.						Calculated to author's groups.	
	I.	II.	III.	IV.	V.	Non- fila- ment.	Fila- ment.
1. Typhoid fever	54	31	15	0	0	38	32
2. Scarlet fever	44	43	13	0	0	31	39
3. Measles	45	39	16	0	0	31	38
4. Erysipelas	45	40	14	1	0	31	38
5. Diptheria	41	39	17	3	0	29	41
6. Rubella	30	35	32	3	0	21	49
7. Variola	33	35	28	4	0	23	47
8. Pertussis	34	39	27	0	0	24	46
9. Puerperal sepsis	42	37	21	0	0	29	41
10. Gonorrhea	20	31	40	8	1	14	56
11. Acute poliomyelitis	39	27	27	7	0	27	43
12. Dental sepsis	26	38	30	6	0	18	52
13. Cerebrospinal fever	40	45	14	1	0	28	42
14. Septicemia	64	36	0	0	0	45	25
15. Osteomyelitis	47	41	12	0	0	33	37
16. Chronic nasal catarrh	28	31	37	4	0	20	50
17. Lobar pneumonia	57	26	15	2	1	40	30
18. Chronic bronchitis	25	45	23	7	0	18	52
19. Pulmonary tuberculosis	34	44	18	4	0	24	46

In Table V are a few of our own counts showing the relative number of young and old forms by our method where there was an increased number of total leukocytes:

TABLE V.

	Total white blood cells.	Non- filament poly- morpho- nuclears.	Filament poly- morpho- nuclears.	Lymph- ocytes.	Mono- cytes.	Eosino- phils.	Baso- phils.
1. Streptococcic septicemia .	18,000	51	15	15	19	0	0
2. Acute rheumatic fever .	12,100	21	35	26	18	0	0
3. Acute arsenical dermatitis	14,200	35	53	7	5	0	0
4. Lobar pneumonia . . .	61,000	59	37	3	1	0	0
5. Acute hepatitis . . .	14,400	45	7	33	14	0	1
6. Lobar pneumonia . . .	27,800	60	28	10	2	0	0
7. Lobar pneumonia . . .	15,900	39	38	20	4	0	0
8. Subacute sinusitis . . .	12,200	22	44	19	13	2	0
9. Lobar pneumonia . . .	13,000	62	23	8	7	0	0
10. Lobar pneumonia . . .	14,100	80	10	7	3	0	0

The following brief history illustrates the value of the young polymorphonuclear leukocyte count in focal infections: Mrs. H. was admitted to the hospital suffering from a severe incapacitating sciatic neuritis. Roentgen ray films were made of the vertebrae, the pelvic bones, the teeth, and the nasal sinuses. Consultations were had with an orthopedic surgeon, a general surgeon, a dentist, a gynecologist, a specialist in diseases of the nose and throat, and an internist. The reports from these various examinations were entirely negative. The conviction that the patient had an area of focal infection which had been overlooked was strengthened by the fact that counts by three different individuals had shown nonfilament polymorphonuclear leukocytes of 31 per cent, 32 per cent and 34 per cent respectively. The total leukocyte counts were normal. The patient had no fever. Roentgen ray films accordingly were again made of the teeth. The report on the second examination was that a definite abscess was present at the apex of the first lower left molar tooth. This typifies many instances in which we have found the count of assistance in the diagnosis of cryptic infections. Had it not been for the definite increase in nonfilament forms, we would have concluded wrongly that the patient was suffering from a traumatic neuritis.

Summary. We believe that the most delicate method of studying the reaction of the bone marrow in infections of all types is the estimation of the young forms of polymorphonuclear neutrophils. This is in agreement with others. It is especially valuable in the diagnosis of cryptic infections of subacute or chronic types where there is no increase in the total leukocyte count. It may add additional presumptive evidence in cases of malingering and hysteria

masquerading as organic disease. Its value in prognosis is yet to be established. In profoundly toxic cases with a normal total count or a leukopenia, the agonized efforts of the bone marrow can be determined only by study of the character of the nucleus of the leukocyte.

Our method, stated briefly, is the differentiation of 100 consecutive leukocytes to determine thus the percentage of nonfilament neutrophils, filament neutrophils, lymphocytes, monocytes, eosinophils, and basophils, in which Cooke's criterion is used to separate the polymorphonuclear neutrophils into old and young groups. We wish to emphasize that this method is recommended especially for routine clinical examinations and not in competition with the more complex methods available to expert hematologists.

We have found by this method that the upper limit of a normal young polymorphonuclear leukocyte (nonfilament) count is in the neighborhood of 16 per cent of cells. The average count in 190 presumably normal adults was approximately 8 per cent. An increased percentage of young polymorphonuclear leukocytes may indicate the existence of infection, even though the total number of leukocytes is not increased.

REFERENCES.

Arneth, J.: *Die neutrophilen weissen Blutkörperchen bei Infektionskrankheiten*, Gustav Fischer, Jena, 1904.

Cooke, W. E., and Ponder, E.: *The Polynuclear Count*, Charles Griffin & Co., London, 1927.

Piney, A.: *Recent Advances in Hematology*, P. Blakiston's Son & Co., Philadelphia, 1928.

Pons, C., and Krumbhaar, E. B.: *Studies in Blood Cell Morphology and Function; Extreme Neutrophilic Leukocytosis with a Note on a Simplified Arneth Count*, J. Lab. and Clin. Med., 1924, 10, 1.

Schilling, V.: *Das Blutbild und seine klinische Verwertung*, Gustav Fischer, Jena, 1926; also *Ztschr. f. klin. Med.*, 1920, 89, 1.

NOTE ON THE DIAGNOSIS OF PNEUMOCOCCUS PERITONITIS FROM THE BLOOD PICTURE.

BY CHARLES L. GIBSON, M.D.,

SURGEON TO THE FIRST SURGICAL (CORNELL MEDICAL) DIVISION OF THE NEW YORK
HOSPITAL, NEW YORK.

THE behavior of the differential blood count in pneumococcus peritonitis is so characteristic that the diagnosis of this condition can be made or suspected in practically all cases. I have already called attention to this blood count in a paper on pneumococcus peritonitis; but repeat it under a special heading to draw the attention of the profession more specifically to its important diagnostic side and to include two supporting examples.

I reproduce here a tabulation of the blood count in eight cases (Chart I).¹

To emphasize the contrast in nonpneumococcic forms of peritonitis, particularly appendiceal peritonitis, the leukocyte-polymorphonuclear ratio in a group of fatal cases is exhibited (Chart II).

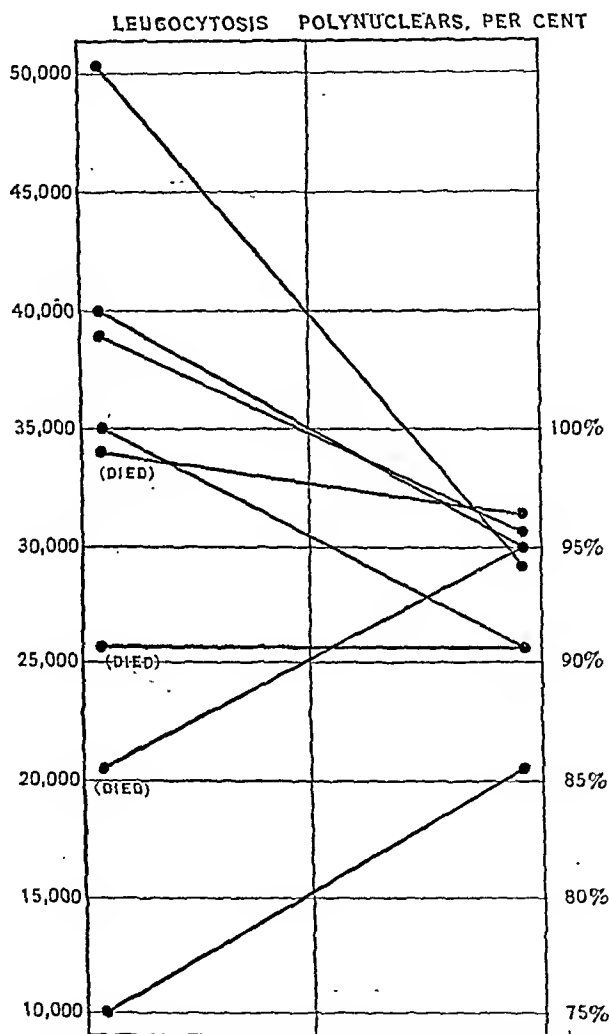


CHART I.—Eight cases of pneumococcal peritonitis.

Contrary perhaps to the general impression, the severe forms of ordinary peritonitis have relatively low leukocytosis with a fairly high polymorphonuclear per cent, whereas in pneumococcus peritonitis we have for the most part an extraordinarily high leukocytosis, as high as 74,000, with a high percentage of polymorphonuclears.

These blood counts are plotted on my so-called "Standard Chart"² where we start a baseline of 10,000 leukocytes, balanced by 75 per cent polymorphonuclears; the maximum normal count.

The differential count shows the tendency of the appendiceal peritonitis to start low down on the chart on the leukocyte side and rise toward the polymorphonuclear, whereas in pneumococcus peritonitis we start high up on the chart on the leukocyte side with a distinct drop toward the polymorphonuclears, which meet approximately at the same point as the ordinary appendiceal peritonitis, say 90 per cent or over.

This is a reaction that is given by nothing else that I know of and, as I repeat again, is so characteristic that the diagnosis should be at once obvious.

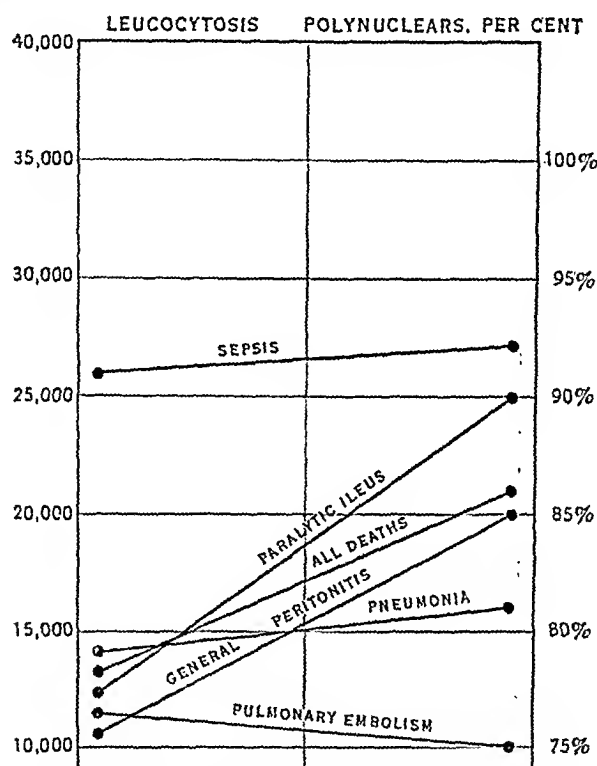


CHART II.—Five cases of nonpneumococcic peritonitis.

Since my paper was published two cases, proved by cultures, (the only criterion) have come under observation. One is in a boy, with secondary pneumococcus peritonitis, subsequent to a respiratory infection. This boy was not operated on, as, the diagnosis having been established, we knew there was no use operating on secondary forms, the only form seen in males. The patient recovered completely. The leukocytosis, 74,000, is the highest we have ever seen (Chart III).

The next case, in a female, making nine cases of primary pneumococcus infection studied, was seen recently in consultation. By primary pneumococcus peritonitis we mean that form of peritonitis where the portal of entry is through the genital tract and of course is seen only in the female, more usually in girls from four to seven

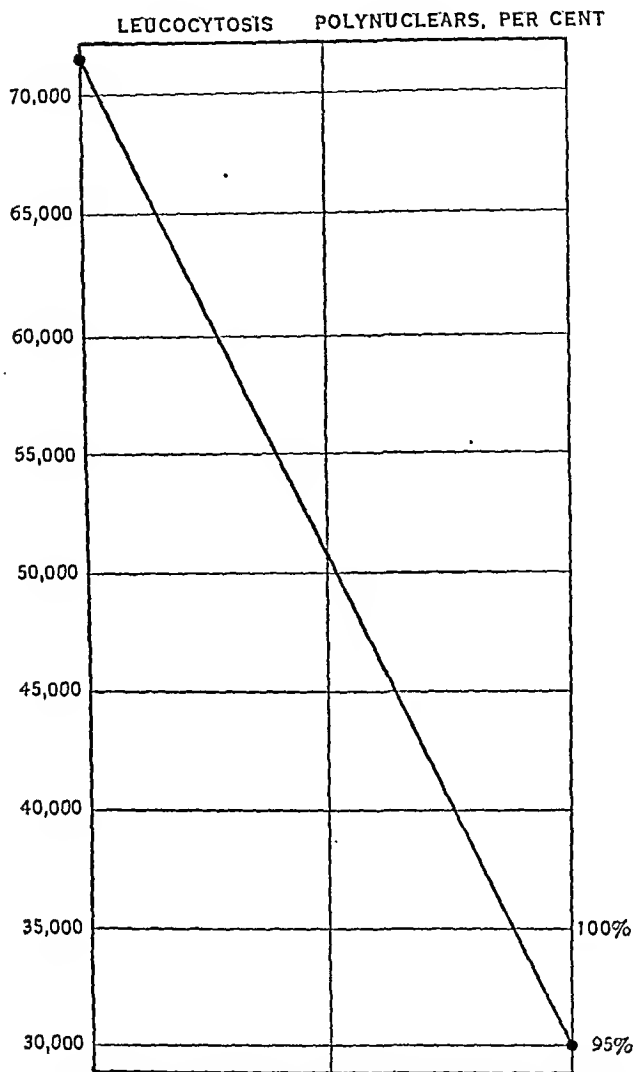


CHART III.—Pneumococcic peritonitis secondary to respiratory infection.

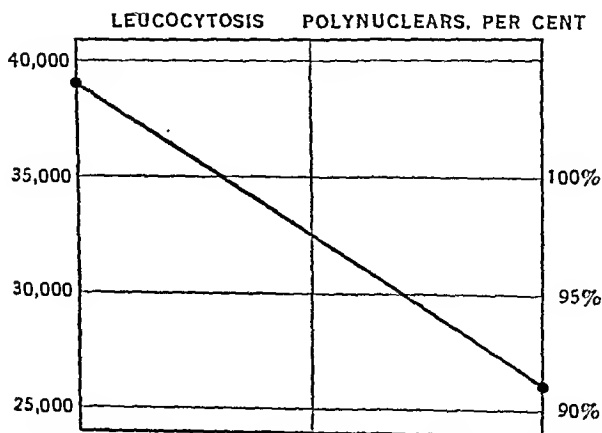


CHART IV.—Primary pneumococcic peritonitis.

years of age. A glance at the temperature chart, which showed an irregular temperature running for weeks, and the first differential count, namely 39,000 leukocytes and 92 per cent polymorphonuclears (Chart IV), allowed me to establish without hesitancy the diagnosis of primary pneumococcus peritonitis, which was verified at operation.

Pneumococcus peritonitis, while uncommon, is by no means rare, and can be easily recognized with realization of the significance of this absolutely characteristic blood picture.

Summary. In pneumococcic peritonitis the characteristic picture of an extraordinarily high leukocyte count with high percentage of polymorphonuclears is a valuable point in differential diagnosis from appendiceal and other nonpneumococcic forms of peritonitis.

In "Standard Blood Charts" this is brought out by a descending rather than an ascending curve.

BIBLIOGRAPHY.

1. Gibson, C. L.: *Pneumococcus Peritonitis*, 1925, 43, 22.
2. Gibson, C. L.: *The Value of the Differential Leukocyte Count in Acute Surgical Disease*, *Ann. Surg.*, 1906, 43, 485.

STUDIES CONCERNING DIGITALIS THERAPY IN LOBAR PNEUMONIA.*

BY WALTER L. NILES, M.D.,

PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY.

AND

JOHN WYCKOFF, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, NEW YORK UNIVERSITY, NEW YORK CITY.

ALTHOUGH many authors have expressed opinions concerning the therapeutic value of digitalis in lobar pneumonia, review of the literature fails to reveal any studies which present definite evidence that the use of the drug modifies the mortality of the disease. While a few observers, notably Carhart,¹ Sir James Mackenzie,² Brunton,³ Hare,⁴ and Stuart Hart⁵ have either opposed or have expressed little enthusiasm for the use of digitalis in pneumonia, most authors have favored its administration. Burrage and White,⁶ in 1927, studied the records of 221 cases of lobar pneumonia in the Massachusetts General Hospital and reported that no untoward effects from a toxic action of digitalis in their series were observed. They concluded that the data suggested that digitalis is of value in pneumonia when given in sufficient dosage, but that the cases were inadequate in number to prove the matter. Among those who have

* Read at the Association of American Physicians, Atlantic City, N. J., May 5, 1930.

advocated the routine use of digitalis in pneumonia are Stone, Phillips and Bliss,⁷ who studied records of the U. S. Army Base Hospital at Fort Riley, Kansas. Stone⁸ subsequently analyzed the records in greater detail and added to the number of digitalis treated cases, as the result of which he advanced data favoring the beneficial effects of digitalis in the pneumonias without sepsis. Brooks and Carroll⁹ analyzed 5000 protocols of cases dying in the American Expeditionary Forces in France and concluded that routine digitalization was beneficial in the older age groups. In neither of these series was there an unselected group of untreated controls observed simultaneously with and under identical circumstances as the digitalis-treated cases. A group of control cases is of course essential for sound conclusions. The analysis of hospital records of previous years with the division of cases into digitalis untreated and treated groups does not constitute a properly controlled series, for as a rule, under these circumstances the milder cases receive no digitalis, while the more severe cases are thought to need and are given digitalis. This fact is well brought out by Randolph¹⁰ in his analysis of 100 consecutive cases at the George Washington University Hospital and by Cohn and Jamieson¹¹ in their study of 105 cases at the Hospital of the Rockefeller Institute, and also by Burrage and White⁶ in their analysis of cases at the Massachusetts General Hospital. The method of Hart, in his study of influenzal pneumonia in which a considerable number were selected at random from time to time, does not satisfy one. Neither does the comparison of untreated cases observed during one period of time with cases treated with digitalis during another period seem justified, as was done by Stone, Phillips and Bliss, and later again by Stone, when the virulence of the infecting organisms admittedly differs from time to time.

The observation that digitalis failed to slow the heart in fevers led many clinicians to doubt if it produced any effect in pneumonia. In 1917 Cohn and Jamieson demonstrated that the drug produced in the pneumonia heart the same electrocardiographic changes that were found in normal controls. Cohn¹² had concluded in 1916 "that digitalis did not harm and it might be life saving" and reported that, therefore, digitalis was given to all pneumonia patients at the Hospital of the Rockefeller Institute as a routine. Since that time it has been widely used in pneumonia, and has generally been given as a routine on the three Medical Divisions of Columbia University, Cornell University and New York University at Bellevue Hospital. The attending physicians, however, were doubtful of its effect on the mortality rate and believing that unusual opportunities for further study were available at Bellevue Hospital, in 1927 formed a committee (a) to organize and supervise a study of the effects of digitalis in pneumonia. The observations were carried on continuously throughout the years 1928 and 1929 and are the basis for this report.

The University services at Bellevue Hospital were believed to present unusual advantages for such a study: (1) For the reason that a large number of cases could be observed; (2) for several years cases of lobar pneumonia had been treated with specific antipneumococcus serum on a carefully controlled plan with untreated control cases equal in number to those treated, and (3) because interest and study in the use of digitalis in heart disease has been a tradition on these services for fifty years.

In accordance with the plan already in operation, patients were admitted into the pneumonia series according to the date and hour of admission, alternate cases being treated with serum. The combination of serum and digitalis therapy led to the grouping of these patients into four classes, selected only by the time of admission, and were designated Classes A, B, C and D, two of which were controls and two treated, with reference to each type of treatment. Thus:

Class A received neither serum nor digitalis.

Class B received serum only.

Class C received digitalis only.

Class D received both serum and digitalis.

This system of classification operated on each ward independent of other wards so that factors of general care and nursing might be the same for each class of treatment.

During the first year of the digitalis study all cases of lobar pneumonia were included in the series regardless of the duration of the disease or the presence of systemic complications. In the second year those who gave a history of more than eight days duration and those with general systemic diseases were excluded from the digitalis serum series.

Exactly similar observations were made on the control and on the treated patients. In addition to the usual clinical and laboratory examinations an electrocardiogram was made daily during the febrile period and on alternate days thereafter. A control record was made on all digitalis-treated patients before any digitalis was administered. In the first year, 2668 electrocardiograms were taken and in the second year 3369. Of the 835 cases studied in both years, 625 or over seven-tenths were electrocardiographed three or more times, about two-tenths had one or more tracings; 57, or less than one-tenth, died before any records could be obtained.

Precautions were taken to insure accurate administration of the digitalis at the time ordered. The digitalizing dose of each patient was put in a small cardboard box by the physician in charge, labeled with his or her name and given to the nurse in charge of the ward. The order for digitalis was written in the ward order book and also on a manilla tag which was fastened to the patient's bed. When the nurse gave the digitalis she initialed the tag and noted the hour. These tags were collected later and constitute a permanent record.

In addition to the regular professional staff, a full-time Fellow (b) was assigned to supervise the digitalis treatment. He was assisted by an electrocardiographic technician and a diener. Another full-time Fellow gave the serum treatment and was in charge of the bacteriological work.

Upon beginning the study it was decided to continue to employ on each Medical Division that preparation of digitalis which had previously been in routine use, namely, one commercial preparation, termed Specimen B, on the First and Second (Columbia and Cornell) Divisions, and another commercial preparation, termed Specimen A, on the Third (New York University) Division. Both preparations had been standardized by the manufacturers by the cat method of Hatcher. Specimen A was reported to have a potency of 100 mg., equivalent to one cat unit; the other, Specimen B, of 66 mg., equivalent to one cat unit. Having been in routine use in the wards there was at that time no reason to doubt the reliability of their standardization. However, it was later noted that there was a high incidence of toxic signs in patients treated with the B preparation, and it was subsequently found that this specimen of digitalis was approximately twice as active as the manufacturer had stated in terms of cat-unit potency. A preliminary report¹³ dealing with the standardization of this preparation has been published, and a more detailed article is in the hands of the publishers. When the error in standardization had been proved, a third, non-commercial, standardized preparation of digitalis was used, and was administered on all the divisions.

It was realized that in an acute disease like pneumonia the patients should receive their digitalis rapidly. At the same time it was felt that the production of toxic effects should be prevented if possible. For this reason it was decided to give the digitalis in divided dosage and in no case to give a patient a digitalizing dose of more than 0.15 of a cat unit per pound of body weight, and to stop the administration of the drug before this amount was given if toxic symptoms were observed. During the first year the dose was divided into parts approximating 30 per cent, 30 per cent, 15 per cent, 15 per cent and 10 per cent of the estimated dose and these were given at intervals of six hours, the last dose (when given) being given about twenty-four hours after the first. As it was deemed unwise and unnecessary to weigh the patients, they were divided roughly into three groups: those who appeared to weigh less than 125 pounds, those weighing between 125 and 175 pounds and those weighing over 175 pounds.

Because of the incidence of toxic signs, especially vomiting and the higher grades of heart block, in the digitalis-treated cases, it was decided in the second year of the investigation to reduce the dosage to nearly half. Patients were then divided into two weight groups instead of three, namely, above and below 150 pounds. The

lighter weight group received a total digitalizing dose of 10 cat units, or 1 gm., and the heavier, of 12.5 cat units, or 1.25 gm. This was administered in three doses, the first, 50 per cent of the total, the second 25 per cent given twelve to eighteen hours after the first; and the third dose, 25 per cent, given after another interval of six to eight hours.

A daily maintenance dose of 2 cat units was given in both years. This was administered in a single dose each morning, and was discontinued when the temperature became normal or when toxic signs developed.

The data which were collected during the two-year period of this investigation have been studied recently. We will present at this time a summary of the results according to the factors which are known materially to affect the mortality rate in lobar pneumonia, namely: sex, age, pneumococcus type and the severity of the infection as indicated by septic complications and positive blood cultures. More detailed studies will be published subsequently.

TABLE I.—COMPARATIVE MORTALITY OF DIGITALIS CONTROL AND TREATED CASES FOR THE FIRST AND SECOND YEARS OF THE INVESTIGATION.

Year	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
First	197	68	34.5	158	67	42.4	7.9
Second	207	68	32.9	180	73	40.6	7.7
First and second	404	136	33.7	338	140	41.4	7.7

Table I shows that although the mortality rate was slightly higher in both the control group and the digitalis-treated group in the first year of the study the differences in the mortality rate for both years were remarkably similar. It indicates that for every 100 cases in the control group that died there were 122 fatalities in the digitalis-treated group.

TABLE II.—COMPARATIVE MORTALITY OF PATIENTS RECEIVING DIGITALIS A, B AND G AND OF CONTROL PATIENTS.

Digitalis.	No. of cases.	No. died.	Mortality, per cent.
A	90	33	36.7
B	142	67	42.2
G	106	40	37.7
Controls	404	136	33.7

Table II shows the number of cases and the mortality according to the preparation of digitalis which was given. As stated above, due to erroneous standardization of Specimen B, patients treated with this preparation received approximately twice the estimated dose calculated by the body-weight method. Specimen A was administered in the correct dosage. Specimen G was given entirely in the smaller dosage, approximately one-half of the total digitalizing dose as calculated by the body-weight method.

It may be seen in Table II that the percentage mortality of the cases treated with Specimen B is 13.5 higher than of the control group. Or it may be stated that for every 100 control patients that died there died 140 patients treated with Specimen B. The differences in percentage mortality between cases treated with Specimen A and G and the control group is only 3.0 and 4.0 respectively.

Specimen B was administered to 63 per cent of all digitalis-treated cases in the first year and to only 30 per cent of all digitalis-treated cases in the second year; also the group which was given Specimen G received much smaller doses as described before. It is therefore of interest to recall Table I, which gives comparisons with the control group in each year. It showed that the difference in percentage mortality is practically the same in each year. Therefore one may conclude that over-dosage with digitalis is not the sole cause for the higher mortality rate of the digitalis-treated group.

TABLE III.—MORTALITY OF MALES AND FEMALES FOR DIGITALIS CONTROL AND TREATED PATIENTS.

Sex.	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
Male . . .	357	123	34.5	299	125	41.8	7.3
Female . . .	47	13	27.7	39	15	38.5	10.8

Table III deals with the factor of sex and shows that the mortality rate is higher for both sexes in the digitalis-treated groups as compared with that of the controls. The difference in mortality shown in Table I cannot, therefore, be due to a preponderance of males, which sex always gives a higher mortality than do females.

TABLE IV.—MORTALITY OF AGE GROUPS FOR DIGITALIS CONTROL AND TREATED PATIENTS.

Age group in years.	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
10 to 29 . . .	94	15	16.0	73	19	26.0	10.0
30 to 39 . . .	109	30	27.5	76	25	32.9	5.4
40 to 49 . . .	99	40	40.4	99	44	44.4	4.0
50 plus . . .	102	51	50.0	90	52	57.8	7.8
Totals . . .	404	136	33.7	338	140	41.4	7.7

Age is well known to influence mortality in pneumonia, the older groups showing a higher death rate than the younger groups. Table IV shows that the mortality of the digitalis-treated cases is higher than that of the corresponding controls in both the older and the younger groups. Therefore, a preponderance of old patients in the digitalis-treated group is not an explanation for the higher mortality rate in the treated cases shown in Table I.

TABLE V.—MORTALITY OF PNEUMOCOCCUS TYPES FOR DIGITALIS CONTROL AND TREATED CASES.

Type.	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
I	98	22	22.4	66	23	34.8	12.4
II	130	62	47.7	108	49	45.4	-2.3
III	28	9	32.1	25	12	48.0	15.9
IV to XIII and unclassified . . .	135	33	24.4	128	50	39.1	14.7
Miscellaneous . .	13	10	11	6		
Totals . . .	404	136	33.7	338	140	41.4	7.7

Table V analyzes the factor introduced by variation in the virulence of the specific pneumococcus types. It shows that in all types, except Type II, the mortality of the digitalis-treated cases is higher than that of their controls.

TABLE VI.—MORTALITY OF PNEUMOCOCCUS TYPES BY AGE GROUPS FOR DIGITALIS CONTROL AND TREATED GROUPS.

Type.	Age in years.	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
		No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
I	10 to 39 . .	62	6	9.7	33	6	18.2	8.5
	40 plus . .	36	16	44.4	33	17	51.5	7.1
II	10 to 39 . .	53	21	39.6	54	17	31.5	-8.1
	40 plus . .	77	41	53.2	60	36	60.0	6.8
III	10 to 39 . .	11	1	9.1	9	4	44.4	35.3
	40 plus . .	17	8	47.1	16	8	50.0	2.9
IV to XIII and unclassified:								
	10 to 39 . .	72	12	15.5	53	15	28.3	12.8
	40 plus . .	63	21	33.3	75	35	46.7	13.4

Table VI subdivides the pneumococcus types into younger and older-age groups. It reveals that the single exception regarding the higher mortality in the digitalis-treated cases is found in the younger age group with Type II pneumococcus infections. No explanation has been found for this exception. However, if all cases which were admitted to the series (not excluding cases discharged at their own risk, cases in the C and D series which received no digitalis, and deaths occurring within twenty-four hours after admission) are analyzed, we find that, in common with all other types, the mortality of the digitalis-treated group in Type II infections is higher than in the control group.

The factor of virulence may possibly be measured by the incidence of septic complications. Again this factor is found not to influence the relative mortality of the control and digitalis-treated cases.

It was suggested that if the cases with septic complications were excluded from the series a better comparison could be drawn of the mortality in the control and digitalis-treated cases. Table VIII

makes a comparison of the mortality rates of the presumably milder, uncomplicated cases, and the difference between the control and the treated groups is seen to persist.

TABLE VII.—MORTALITY OF CASES WITH SEPTIC COMPLICATIONS FOR DIGITALIS CONTROL AND TREATED GROUPS.

	Digitalis control.		Digitalis-treated.	
	No. of cases.	No. died.	No. of cases.	No. died.
Pneumococcic complication.				
Empyema	13	6	16	11
Endocarditis	1	1	1	1
Pericarditis	3	3	0	0
Meningitis	0	0	4	4
Arthritis, suppurative	0	0	2	2
Lung abscess	2	1	1	1
Otitis media, purulent	5	3	3	0
Totals	24	14	27	19
Mortality	58.3 per cent		70.4 per cent	
Difference in mortality	12.1 per cent			

TABLE VIII.—MORTALITY OF THE GENERAL SERIES EXCLUDING CASES WITH SEPTIC COMPLICATIONS FOR DIGITALIS CONTROL AND TREATED GROUPS.

Group.	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
General Series	404	136	33.7	338	140	41.4	7.7
"Septic" cases	24	14	58.3	27	19	70.4	12.1
Series excluding "septic" cases	380	122	32.1	311	121	38.9	6.8

TABLE IX.—COMPARATIVE MORTALITY OF PATIENTS WITH NEGATIVE AND POSITIVE BLOOD CULTURES FOR DIGITALIS CONTROL AND TREATED GROUPS.

Blood culture.	Digitalis control.			Digitalis-treated.			Difference in mortality, per cent.
	No. of cases.	No. died.	Mortality, per cent.	No. of cases.	No. died.	Mortality, per cent.	
Positive	54	43	79.6	53	42	79.2	-0.4
Negative	124	25	20.2	116	40	34.5	14.3

It may be asserted that cases with frank septic complications do not truly represent all cases of so-called sepsis, such as septicemia in which no localization has occurred and that the cases with positive and those with negative blood cultures form a better basis for comparison. Table IX shows that in the most severe cases, those with positive blood cultures, there is no difference in the mortality rates between the control and digitalis-treated groups, while in the milder cases, with negative blood cultures the mortality is 14.3 per cent higher for the treated group.

TABLE X.—MORTALITY AND INCIDENCE OF AURICULAR FIBRILLATION AND FLUTTER.

Auricular fibrillation and flutter.	Digitalis control (429 cases).	Digitalis-treated (406 cases).	Total, all cases (835 cases).
Number of cases	17	16	33
Incidence in series	4.0 per cent	3.9 per cent	4.0 per cent
Number died	9	14	23
Mortality	52.9 per cent	87.5 per cent	69.7 per cent

Table X shows that the incidence of auricular fibrillation and auricular flutter is the same in the control and the digitalis-treated groups. The mortality is, however, distinctly higher in the digitalis-treated group. Although the number of cases is not sufficient to warrant drawing conclusions the inference is clear. These complications are now being subjected to further study and communications on this subject will be issued subsequently.

Conclusion. Although the Committee would prefer to continue the investigation on the results of digitalis therapy in pneumonia and observe a larger number of cases over a series of years, it was the unanimous opinion of the Committee and its advisers that the results obtained thus far do not justify continuing the routine administration of digitalis to patients suffering with lobar pneumonia.

(a). The committee for the study of digitalis in pneumonia is composed of Drs. Norrie and Woodruff of the First (Columbia University) Medical Division, Drs. Dubois, Niles and Eggleston of the Second (Cornell University) Medical Division, and Drs. Wyckoff and DeGraff of the Third (New York University) Medical Division of Bellevue Hospital.

(b). The Fellows in Medicine in charge of the digitalis investigation were Marjory Shearer, M.D., during the first year, and Janet G. Travell, M.D., during the second year. The authors desire to express their appreciation for the invaluable services rendered by these Fellows.

BIBLIOGRAPHY.

1. Carhart: J. Am. Med. Assn., 1891, 16, 811.
2. Mackenzie: Diseases of the Heart, 2d ed., 1908.
3. Brunton: Therapeutics of the Circulation, 2d ed., London, 1914, p. 281.
4. Hare: Pneumonia: Handbook for Practical Treatment, 1911, 2, 269.
5. Hart: AM. J. MED. SCI., 1919, 158, 649.
6. Burrage and White: AM. J. MED. SCI., 1927, 174, 260.
7. Stone, Phillips and Bliss: Arch. Int. Med., 1918, 22, 409.
8. Stone: AM. J. MED. SCI., 1922, 163, 659.
9. Brooks and Carroll: AM. J. MED. SCI., 1920, 160, 815.
10. Randolph: Arch. Int. Med., 1929, 43, 248.
11. Cohn and Jamieson: J. Exp. Med., 1917, 25, 65.
12. Cohn: New York Med. J., 1917, 105, 234.
13. Wyckoff and Gold: J. Am. Med. Assn., 1930, 94, 626.

BARIUM CHLORID IN THE STOKES-ADAMS SYNDROME OF COMPLETE HEART BLOCK.

NEGATIVE RESULTS IN EIGHT CASES.

BY AARON E. PARSONNET, M.D.,

NEWARK, N. J.,

AND

ALBERT S. HYMAN, M.D.,

NEW YORK CITY.

COMPLETE heart block with auricular and ventricular dissociation has always attracted the attention of clinicians. The peculiar physiologic phenomena occurring in this condition have been a constant source of further investigation both in the laboratory and

clinic. The factors involved in the development of independent auricular and ventricular rhythms have long been known; any process which prevents the excitation wave from completing its journey from the sinoauricular node through the auricular musculature to the auriculoventricular node of Tawara will permit the establishment of an independent ventricular rhythm. We have previously pointed out the life-saving mechanism which is involved in this interplay of the two pacemakers of the heart.¹

Where the ventricular rhythm is regular and the rate averages from 36 or more beats per minute the patient may experience no especial difficulties, and if he lives within the functional capacity of his heart the condition may persist for many years. Mackenzie² watched several such cases for about twenty years. Harris³ reported a case which lived for twenty-eight years; Willius⁴ studied a case fifteen years after its original onset. Wells and Wiltshire's⁵ patient had the condition for twelve years, and Lewis⁶ saw a patient with complete heart block for fifteen years. Two cases under our observation have lived for eleven and eight years respectively.

On the other hand, where there are irregularities of rhythm and when the ventricular rate is so slow that the development of the Stokes-Adams syndrome is present or imminent a frantic search for remedies must be made, more especially if the seizures are frequent. The past decade has seen many modes of therapy recommended for the relief of this serious phase of complete heart block. Wenckebach showed that after a simple exercise test a complete heart block might be temporarily broken up; an increase in the circulation of the conducting system area of the heart was said to enhance the probability of conduction. In such cases Phear and Parkinson⁷ demonstrated, in 1922, that adrenalin, injected either subcutaneously or intravenously, exerted a favorable effect upon the convulsive seizures due to the Stokes-Adams phenomenon. Prior to this, in 1916, Danielopolu⁸ reported the experimental use of adrenalin for the relief of unconsciousness due to cerebral anemia from the slowly acting ventricle of complete heart block.

Whether adrenalin enhanced conductivity by increasing the circulation of the bundle system through vasodilatation of its intrinsic vessels as suggested by Cushny,⁹ or whether it is due to stimulation of the sympathetic nerve endings in the auriculoventricular bundle with subsequent improvement of conductivity as maintained by Routier,¹⁰ certain it is that adrenalin exerts a definite though brief action in this condition.

Atropin, when used in large doses, has in certain cases been apparently of value; where the Stokes-Adams syndrome is dependent upon overactivity of the vagus so that conductivity of the bundle system is inhibited the belladonna derivatives may prove to be a physiologic antidote. From a clinical point of view, however, little if any relief has been secured from this remedy. Herman and

Aschman,¹¹ in a study of atropin in complete heart block, have found it to be of slight symptomatic value for the relief of syncope even if there was an increased auricular rate.

Many other drugs from time to time have been suggested; thyroid gland substance or its chemical derivative, thyroxin, has recently been again urged in this condition. Drake¹² reported some success with the administration of this substance in a case of complete block with the Stokes-Adams syndrome. Blackford and Willius,¹³ as long ago as 1917, reported favorable results obtained in 4 cases of this type treated by injections of thyroxin. Even digitalis, the use of which has been theoretically barred in any condition of depressed conductivity, has been shown by Erlanger¹⁴ to be of value in cases of heart block due primarily to insufficient coronary circulation. Where congestive failure has rendered the junctional tissue relatively unresponsive, digitalis, by improving the nutritional state of the myocardium in general, can exert a benign influence.

Much controversial opinion has been expressed for and against numerous other incidental agents which have been reported from time to time in isolated instances; in view, however, of the unreliable results obtained from the more commonly used remedies already mentioned, this is unavoidable and the quest for a specific agent is still in progress. Apparently many drugs offer relief under certain ill-defined conditions occurring simultaneously with the Stokes-Adams syndrome as it is seen in complete heart block. The nitrites, theobromin, euphyllin, alpha-lobelin, cardiazol, coramin, camphor and even dextrose have been reported serviceable.

Finally, the salts of barium and calcium have been suggested. Based upon the well-known experimental work of Rothberger and Winterberg,¹⁵ conducted on dogs and controlled by electrocardiographic studies, it was shown that both drugs increased the irritability of the cardiac muscle. In 1923 Wilson and Herman¹⁶ reported the first clinical use of barium chlorid for the relief of the Stokes-Adams syndrome. Following this, Cohn and Levine¹⁷ gave their experiences in 3 cases where barium chlorid was given by mouth. Levine subsequently collected 2 additional cases¹⁸ and later a third¹⁹ case which received adrenalin intracardially, together with barium chlorid by mouth.

The favorable results in these cases have been confirmed by others; Parsons-Smith,²⁰ Strauss and Meyer²¹ and Price and Nisse²² have obtained various degrees of success with barium chlorid. On the other hand, Heard, Marshall and Adams²³ were not favorably impressed by the action of barium chlorid in their patient.

The rationale of barium chlorid therapy for the prevention and relief of the Stokes-Adams syndrome that is due to complete heart block is based upon the increase in the irritability curve of the ventricle when the drug is given in sufficiently large doses. It has

also been shown that the degree of resistance offered to the excitation wave as it approaches the atrioventricular junction of the heart is decreased almost to the same extent as the increase in the irritability of the myocardium. These two factors, while producing the same ultimate effect, are concerned with two different functions of the heart. From a theoretic point of view, either of these processes if effective will permit previously blocked impulses to pass through from the auricle to the ventricle and would assure the reestablishment of a normal auriculoventricular rhythm. On the other hand, when the irritability curve is increased the ventricles may go into such a state of sensitivity that ventricular fibrillation may develop. Such attacks of ventricular fibrillation have been reported from time to time. With this as its only contraindication, many authors have recommended barium chlorid for Stokes-Adams seizures.

We, however, have been unable to confirm the uniformly effective results of previous investigators. In the close scrutiny demanded of any new remedy, negative findings may often be of greater significance in the total estimation of therapeutic value than the occasional confirmatory reports. This holds true of any new therapeutic agent; Puckner and Leech²⁴ and Leake²⁵ have stressed this as one of the cardinal requisites in appraising an acceptable new remedy.

We have been interested in the use of barium in a series of 8 cases of complete heart block complicated by the Stokes-Adams syndrome. In none of these cases were we able to obtain any semblance of pharmacologic or physiologic action either good or bad. Special attention was focused upon the quality and the source of barium employed; through the courtesy of a pharmaceutical laboratory in Newark, N. J., a standard tablet containing 0.04 gm. of chemically pure barium chlorid was prepared. These tablets were readily soluble in water and conformed to the standard fragility tests.

Amounts varying from 0.04 to as much as 0.6 gm. were given in twenty-four hours; these doses were continued in various cases from one week to three months and electrocardiographic control of each case was made every two weeks to two months. Full coöperation of the patients was secured by informing them of the experimental character of this remedy, and they were instructed to report immediately upon the development of any new or unusual symptoms. In the period of over three years during which this study was continued only twenty-one emergency calls were made, most of which had no relation to the patients' cardiovascular condition. During the same period 2 patients have died, both of whom were subject to severe Stokes-Adams attacks and in whom there was extensive involvement of the coronary arteries.

A brief résumé of these 8 cases follows:

Case Reports. CASE I.—A. E., male, aged fifty-six years, baker, up to the age of fifty-two the patient had pursued an active and vigorous life. At that time he began to complain of stenocardia which prevented him from

continuing his occupation. The anginal seizures were at first easily controlled by the use of theobromin, but two years later the attacks had become very severe and rendered the patient bedfast. The attacks then disappeared and the patient was able to move cautiously around the house. While sitting in a chair one day he was seen to fall forward and dropped unconscious upon the floor; the family physician, on his arrival found that the patient had recovered consciousness but was still mentally confused. Physical examination at that time showed the pulse to be extremely slow, averaging from 26 to 32 beats per minute. The blood pressure was 100 systolic and 60 diastolic and the heart sounds were of very poor quality. During the next few months he had several such fainting spells, the last of which was so severe that the patient remained unconscious for almost an hour. On the following day he was referred to one of us for cardiovascular study.

Electrocardiographic examination (Fig. 1) revealed a complete auricular and ventricular dissociation; the ventricular rate was rather regular at 26 beats per minute, with an auricular rate of about 72. There were *T*-wave alterations in all leads suggesting considerable coronary artery involvement. There was no axial deviation of the heart but there were apparently two centers for the origin of the ventricular beat.

The general physical examination showed the typical change seen in advanced myocardial disease: the patient was dyspneic, his mucous membranes were cyanotic and he had the peculiar pallor so often seen in coronary disease. The heart was greatly enlarged and the cardiac impulse almost imperceptible. The liver was not enlarged but a slight pretibial edema was present. The Wassermann was negative.

A diagnosis of Stokes-Adams syndrome as a result of complete heart block was made and the patient was placed upon moderately large doses of euphyllin. The attacks continued to occur, however, with alarming regularity and after a six weeks' trial with this drug it was abandoned. Adrenalin was used frequently during the attacks with inconstant results; sometimes the patient could be restored to consciousness within half a minute, at other times 2 and even 3 injections were apparently without effect, the patient returning to consciousness spontaneously.

On October 10, 1928, the patient was first placed upon barium chlorid therapy. The standard tablets containing 0.04 gm. were given three times a day; this quantity was cautiously raised over a period of two weeks to two tablets every four hours for 6 doses, representing 0.32 gm. in twenty-four hours. This amount was then continued over a period of twenty-one days making a total of 8.48 gm. for the first month. During this time no effect directly attributable to the barium was noted. Electrocardiographic studies remained unchanged and clinically the patient continued to have his convulsive seizures. Treatment was then stopped for about ten days during which time the patient was taken to Lakewood, N. J. While there he had two severe attacks which so alarmed his relatives that he was promptly returned home. On close questioning it was found that these attacks were no more severe, perhaps, than those occurring while under barium therapy. The patient expressed the belief that barium seemed to help him so that he was again placed on 0.32 gm. per day. This amount he continued to take until March 3, 1929, a period of 126 days, during which 40.32 gm. of barium were taken altogether.

On that latter date he had an attack so severe that even an intracardiac injection of adrenalin failed to arouse him. His pulse at the wrist was imperceptible and the heart sounds were very weak and irregular at a rate estimated to be about eight or nine beats per minute. With the onset of pulmonary edema, vomiting took place and the patient promptly became unconscious. He was now confined to bed with infrequent attacks for the next two

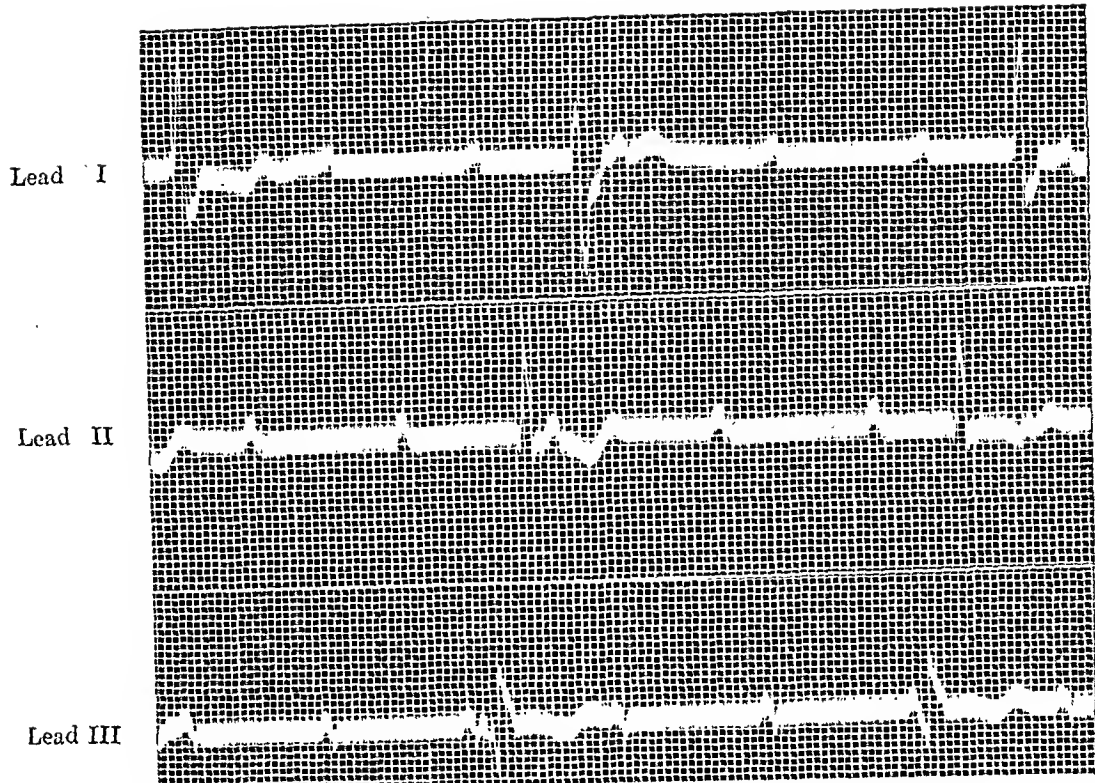


FIG. 1.—Complete heart block; in Lead I note accessory center of origin of the ventricular beat.

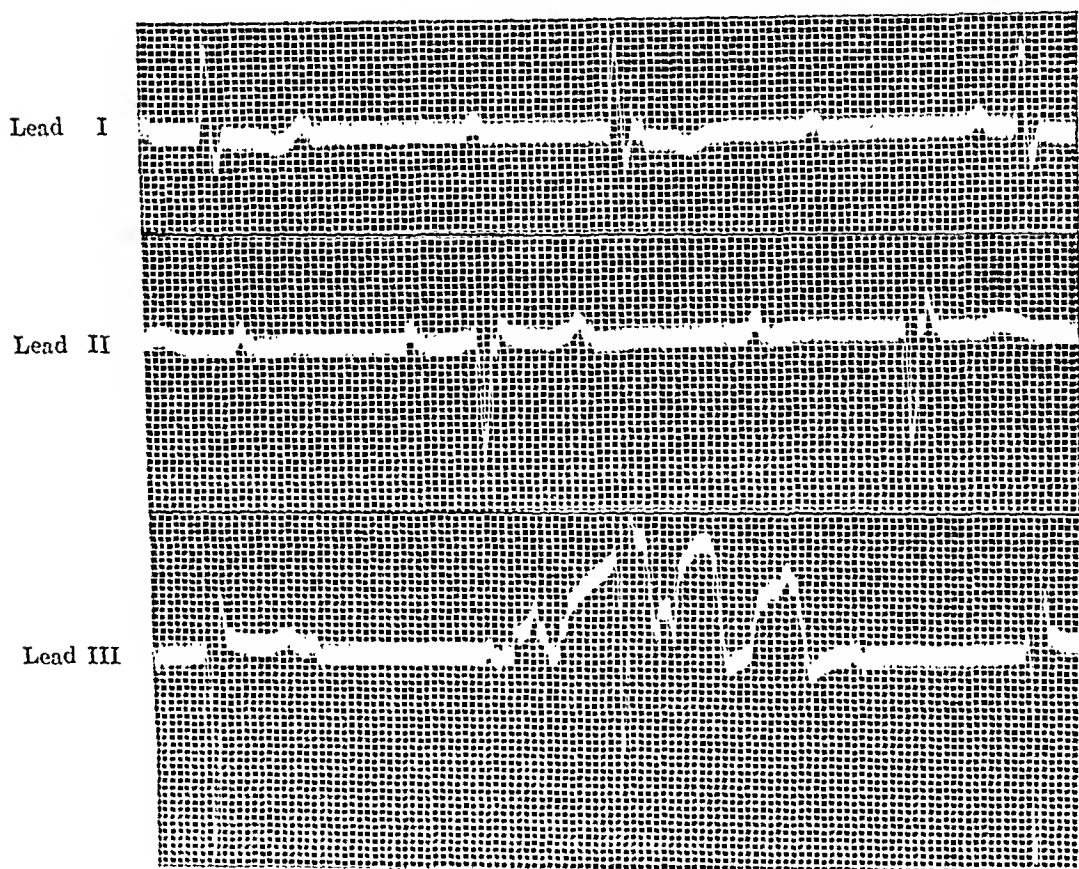


FIG. 2.—Same case. Electrocardiographic records taken one week prior to sudden death. Note short period of ventricular fibrillation in Lead III.

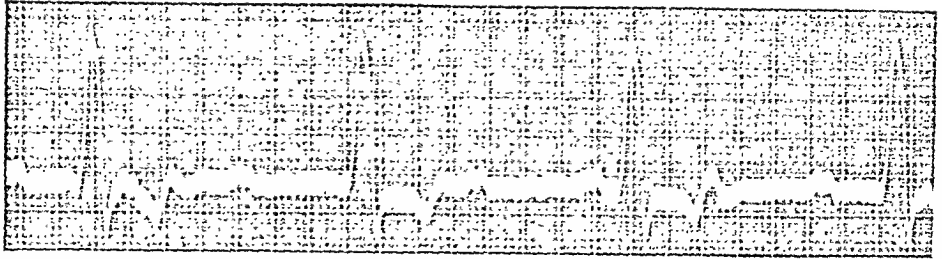


FIG. 3.—Lead I. Complete auricular and ventricular dissociation with right bundle-branch block. Note the rapid ventricular rate.

Lead I

Lead II

Lead III

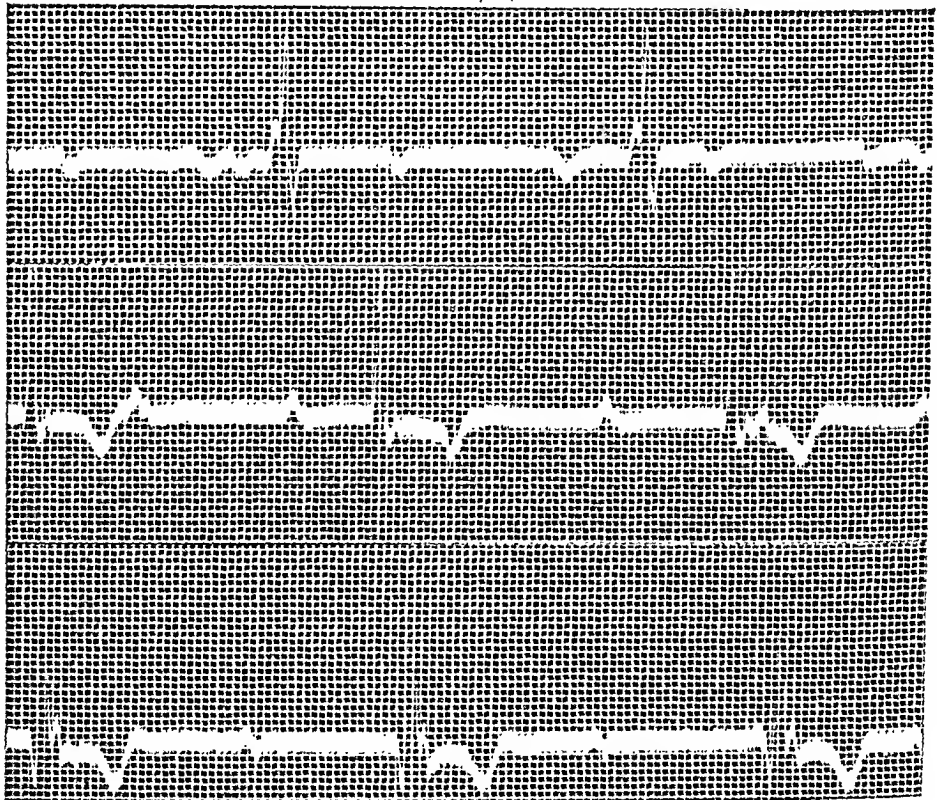
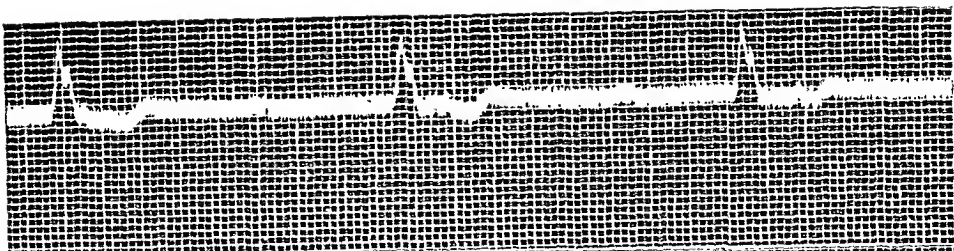
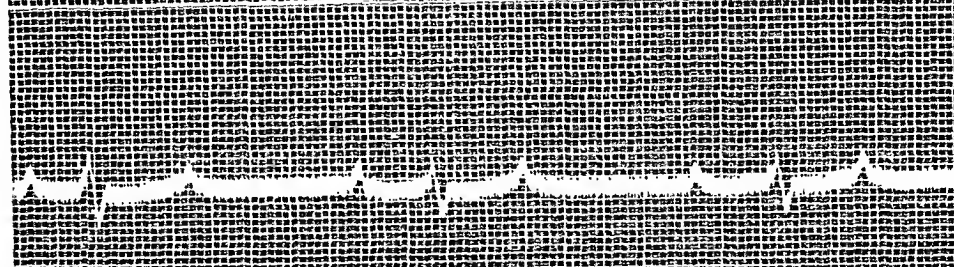


FIG. 4.—Auricular and ventricular dissociation with no axis deviation. Previous records showed a well-marked left axis deviation.

Lead I



Lead II



Lead III

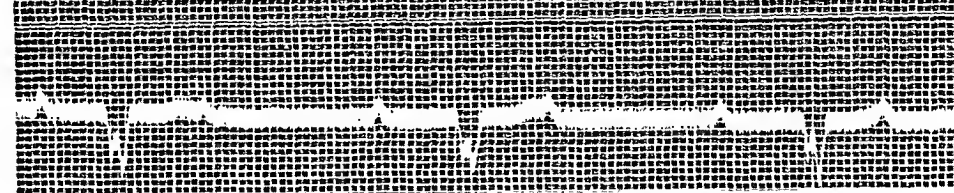


FIG. 5.—Complete heart block with right bundle-branch involvement.

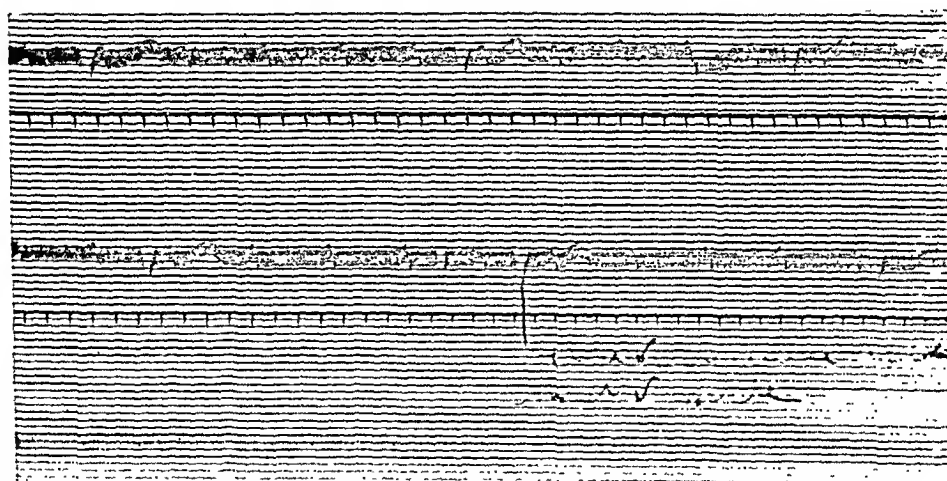


FIG. 6.—Electrocardiographic studies made in London by Sir James Mackenzie in 1922.

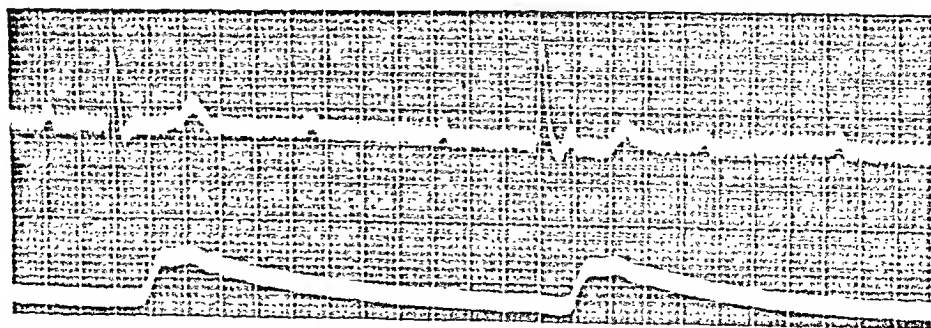


FIG. 7.—Simultaneous electrocardiographic and polygraphic studies made in 1928.

months, during which time no barium was given. On July 1 a final electrocardiogram was taken (Fig. 2), the ventricular rate was 28 beats per minute and the auricular rate was about 66. There were *T*-wave changes now only in the first lead, but there was a well-marked left axial deviation of the heart. During the taking of the third lead a short paroxysm of ventricular fibrillation was detected. One week later, on July 8, while on his way to our office, he dropped dead on the street.

CASE II.—B. D., female, aged sixty years, housewife, following climacteric changes of an unusually stormy type covering a period from the age of forty-seven to fifty-three years, during which time she maintained a persistently marked hypertension, was first seen by us at the age of fifty-seven years. At that time she was exhibiting fully all the after effects of prolonged hypertensive heart disease. Her dyspnea was especially distressing; electrocardiographic studies at this time revealed a marked left axial deviation of the heart with alteration of the *T*-waves in the first and second leads. There was a normal auriculoventricular rhythm. Routine therapy with prolonged bedrest was instituted. About fourteen months later, on March 10, 1927, the patient was seen again: the complaint at this time was the frequently occurring attacks of unconsciousness which developed even during sleep. Diagnosis of the Stokes-Adams syndrome was made upon the discovery of a complete auricular and ventricular dissociation; electrocardiographic studies were corroborative. The patient was immediately placed on six tablets of barium chlorid a day; on April 19, after having taken a total of 9.6 gm. of barium chlorid without any therapeutic improvement, the drug was discontinued. No difference either in frequency or duration of the attacks was observed. The patient is still alive; the attacks are perhaps less frequent than previously and no treatment except mild sedatives has been used for the past year.

CASE III.—W. D., male, aged fifty-nine years, street-car conductor, a man of unusual physique and giving a history of former athletic prowess, having been a hammer thrower, was suddenly stricken on the street with a dizzy spell. This attack was followed in subsequent weeks by similar seizures, some of these accompanied by lapses of consciousness. He came under our observation September 16, 1926, at which time a diagnosis of complete heart block with Stokes-Adams syndrome was readily made.

Electrocardiographic studies (Fig. 3) showed a right bundle-branch block, *T*-wave alterations in Lead I and a complete auriculoventricular dissociation. The auricular rate averaged about 80 and the ventricular rate was constant at 44. This case presents a rather unusual feature, namely, the Stokes-Adams syndrome in a relatively high ventricular rate. Barium therapy was instituted on October 3, 1926; four tablets were given daily until December 27, 1926, a total of 20.5 gm. was given. No appreciable result was noticed and therapy was discontinued.

After three years with little or no drug therapy the patient is still struggling along, dividing his time between chair and bed.

CASE IV.—P. S., male, aged sixty-six years, retired, came under observation on January 7, 1928, with a history of Stokes-Adams seizures for the past year. He had been studied in several clinics in this country and abroad. A large and varied collection of electrocardiographic tracings was presented to us: all were more or less similar and indicated a well established dissociation. This patient had experienced a remarkable array of therapeutic measures, scientific and otherwise, the only omission being that of barium. We considered this an excellent opportunity to demonstrate the efficacy of this remedy. Treatment was promptly started by

giving three tablets a day, which quantity was gradually raised until at the end of a month he was receiving eight tablets a day, which dosage was continued for another six weeks, making a total of 18.24 gm. of barium. To the chagrin of the family and ourselves, no change of any kind was noted and the drug was abandoned. The patient experienced no change in his condition but on December 10, 1928, while at dinner was seized with stenocardial pain and expired in a few minutes.

CASE V.—H. McG., male, aged fifty-one years, former bartender, with a long alcoholic history, negative Wassermann, was previously studied at a local cardiac clinic, where a diagnosis of complete heart block with the Stokes-Adams syndrome was made. The patient was referred to us for barium therapy. We began on May 26, 1929, with six tablets per day and continued on this dosage until August 4, a total of 18.24 gm. of barium having been administered. As in the previous cases, no change in the patient's status could be noticed. His condition at present is much aggravated by frequent attacks of coronary seizures in spite of the large doses of metaphyllin which he has been receiving.

CASE VI.—M. F., male, aged fifty-six years, jeweler, an obese individual weighing 248 pounds, with a long cardiovascular history has been under our care since March 8, 1927. At that time he showed rather typical electrocardiographic findings, a left axial deviation, T-wave alterations, and frequent left ventricular extrasystoles of the fundamental type. A régime of reduction by diet and mild physiotherapy was instituted with rather indifferent results, as the patient was decidedly noneooperative. On June 12, 1928, following a burglar scare at his place of business he was found unconscious on the floor. It was thought that he had been attacked, but the attending physician, noting the extreme bradycardia, made a tentative diagnosis of heart block with the Stokes-Adams syndrome. After a period of hospitalization, during which time complete studies were made, a diagnosis of complete dissociation was confirmed. The electrocardiographic studies were interesting (Fig. 4) in showing not only the block phenomenon but the change in the electric axis of the heart. Where formerly there had been a well marked left axis deviation, now all of the Q-R-S complexes were upright. This observation is not an infrequent occurrence in complete block; many authors have noted the change from a left to a right deviation.

The patient left the hospital on a maintenance dose of twelve tablets of barium daily, the thought being that in an individual of such large proportions a greater dosage might be indicated. On August 2, after having taken 23.52 gm. of barium in forty-nine days, no improvement of any kind was noted. The patient continued to have rather frequent seizures of syncope, some of which were so severe that sphincter control was lost. With a basal metabolic rate of -35 , thyroid was given with a double purpose in view: first, in an attempt to remedy the overweight factor and second, to determine its value in the Stokes-Adams syndrome. Some improvement was noted in both conditions for some time. The patient is still alive, refusing all treatment.

CASE VII.—H. G., aged sixty-eight years, merchant, male, has been known to us for the past seven years, during which time he has always had a bradycardia averaging about 30 to 40 beats per minute. Electrocardiographic studies made in 1923 showed a complete dissociation but the patient experienced no especial difficulties until 1928. He had retired from business and was leading a very regular but inactive life. On February 12, 1928, he suffered his first Stokes-Adams attack which lasted a few minutes; subsequent to this and occurring at more or less regular intervals he was seized

with attacks of syncope which were relieved without special therapy. On July 17, 1928, during a very hot spell, he experienced his worst attack and was unconscious for over an hour. He was given an intracardiac injection of adrenalin which seemed to have been somewhat effective. Of especial interest is the fact that there was no change in the ventricular rate during the period of unconsciousness, although the heart sounds were very much weaker. Barium therapy was instituted the following day and continued until November 10, 1928, a total of eighty-three days during which period 26.56 gm. were given. No therapeutic effect having been secured by this time, treatment with this agent was discontinued.

Electrocardiographic studies which were taken from time to time showed no or very little change (Fig. 5). This is a typical tracing; a right bundle-branch block was always present together with changes of the *T*-waves in Lead I. This patient is still alive and in the past two months bedridden.

CASE VIII.—B. I. W., male, aged fifty-nine years, is extremely interesting in that he is a physician who has studied his own case over a period of about fifteen years. His description of the subjective symptoms for the entire course of his illness are picturesque and can only be related here but briefly. He was told in 1915 that he was suffering from "fatty heart" and high blood pressure: after a prolonged course of digitalis therapy he was forced in 1919 to give up the practice of medicine. In 1922, he was examined by Sir James Mackenzie, and electrocardiographic tracings taken in London (Fig. 6) showed a complete auricular and ventricular dissociation with a ventricular rate of 22 beats per minute. He came under our observation in 1927; he had no especial complaints and was living an extremely cloistered life. He had conducted a number of experiments upon himself and was well versed in cardiovascular literature. He had used no special remedies and was of the opinion that alcohol was of decided advantage in the treatment of heart block. On September 16, 1927, he experienced his first Stokes-Adams attack; it occurred while bending over to lace his shoes. He collapsed on the floor and was unconscious for about ten minutes. During the next two months he had eight such attacks and on November 20, at his request, he was placed on barium medication. At first he received only three tablets a day but this he increased to as high as fifteen. On January 1, 1928, after having taken 16.4 gm. of barium over a period of forty-one days with no change in the character or frequency of the seizures, we agreed to abandon it. He is back to his alcohol with apparent relief, the attacks now occurring about once a month and of shorter duration. He possesses a unique series of electrocardiographic tracings: Fig. 7 is a simultaneous electrocardiographic and polygraphic study.

His ventricular rate now averages about twenty-five beats per minute but at times he said that it has been as low as eighteen.

Summary. Table shows the specific details of barium therapy in 8 cases of auricular and ventricular dissociation exhibiting the Stokes-Adams syndrome. In no case did the barium exert any influence, either good or bad, upon the frequency or severity of the seizures, nor was the progress of the myocardial changes altered.

Barium chlorid was given in doses ranging from 0.16 to 0.4 gm. per day. It was administered in one case as long as one hundred and twenty-six days and in no case less than forty days. The total amount of barium taken altogether varied from 9.6 to 40.32 gm.

SUMMARY OF RESULTS.

Case No.	Sex.	Age.	Dose in 24 hours.	Days given.	Total barium.	Results.
1	M	56	0.320	126	40.32	Died.
2	F	60	0.240	40	9.60	Unimproved.
3	M	59	0.160	79	20.50	Unimproved.
4	M	66	0.320	62	18.24	Died.
5	M	51	0.240	69	18.24	Unimproved.
6	M	56	0.480	49	23.52	Unimproved.
7	M	68	0.320	83	26.56	Unimproved.
8	M	59	0.400	41	16.40	Unimproved.

The series comprised 7 males and 1 female, and the ages varied from fifty-one to sixty-eight years. There were 2 deaths in this series, but neither one of them occurred in a period less than three months after the administration of the barium.

The doses used in our series of cases are far larger and extended over a longer period of time than any previously reported cases. We have been unable to demonstrate any effect from barium chlorid when given by mouth and in doses far in excess of those suggested by authors who have obtained favorable results with this substance in the treatment of complete heart block with Stokes-Adams syndrome.

While this series of 8 cases is not large, Stokes-Adams syndrome is by no means common; we, therefore, feel that the series is extensive enough to challenge the test of barium efficacy.

REFERENCES.

1. Parsonnet, A. E., and Hyman, A. S.: *Applied Electrocardiography*, Macmillan, New York, 1929, p. 70.
2. Mackenzie, James: *Diseases of the Heart*, London, 3d ed., 1921, p. 274.
3. Harris, K. E.: *Notes on a Case of Complete Heart Block of Unusually Long Duration*, *Heart*, 1929, 14, 289.
4. Willius, F. A.: *Ann. Clin. Med.*, 1925, 3, 129.
5. Russel, Wells and Wiltshire: *Lancet*, 1922, i, 984.
6. Lewis, Thomas: *Clinical Disorders of the Heart Beat*, London, 1918, p. 121.
7. Phear, A. G., and Parkinson, J.: *Adrenalin in the Stokes-Adams Syndrome*, *Lancet*, 1922, i, 933.
8. Danielopolu, D., and Danulescu, V. C.: *Soc. de Biol.*, 1916, 79, 861.
9. Cushny, A. R.: *Pharmacology and Therapeutics*, London, 9th ed., 1928, p. 387.
10. Routier, D.: *Compt. rend. Soc. de biol.*, 1915, 78, 375.
11. Herman, G. R., and Ashman, R.: *Am. Heart J.*, 1926, 1, 269.
12. Drake, E. H.: *Am. Heart J.*, 1928, 3, 560.
13. Blackford, J. M., and Willius, F. A.: *Am. J. Med. Sci.*, 1917, 154, 585.
14. Erlanger, J.: *Arch. f. d. ges. Physiol.*, 1909, 127, 77.
15. Rothberger, C. J., and Winterberg, H.: *Arch. f. d. ges. Physiol.*, 1911, 142, 461.
16. Wilson, F. N., and Herman, G. R.: *Arch. Int. Med.*, 1923, 31, 923.
17. Cohn, A. E., and Levine, S. A.: *Arch. Int. Med.*, 1925, 36, 1.
18. Levine, S. A.: *Boston Med. and Surg. J.*, 1926, 195, 1147.
19. Levine, S. A., and Matton, M.: *Heart*, 1926, 12, 271.
20. Parsons-Smith, B. T.: *Proc. Roy. Soc. Med.*, 1927, 20, 23.
21. Strauss, S., and Meyer, J.: *Am. Heart J.*, 1928, 3, 328.
22. Price, F. W., and Nisse, B. S.: *Am. Heart J.*, 1929, 5, 197.
23. Heard, J. D.: Marshall, W. R., and Adams, F. S.: *Am. Heart J.*, 1927, 2, 562.
24. Puckner, W. A., and Leech, P. N.: *J. Am. Med. Assn.*, 1929, 93, 1627.
25. Leake, C. D.: *J. Am. Med. Assn.*, 1929, 93, 1632.

A STUDY OF UNINFECTED MURAL THROMBI OF THE HEART.

BY EARLE A. HARVEY, M.D.,

AND

SAMUEL A. LEVINE, M.D.,

SENIOR ASSOCIATE IN MEDICINE, PETER BENT BRIGHAM HOSPITAL, BOSTON.

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.)

A CARDIAC mural thrombus is an antemortem blood coagulum formed on the inner surface of the heart. It is characterized by being adherent to the endocardium, gray or grayish-red in color, granular, friable and microscopically may show definite organization. It is easily separated from the postmortem or agonal clots, since these usually are nonadherent and are pale, yellowish, smooth, elastic, gelatinous masses which do not show evidence of organization. The present study was limited to uninfected thrombi. Criteria of infection were based on general appearance, cultural and microscopic examination of stained sections and the clinical entity involved.

These thrombus masses in the early days were called polyps because of their similar appearance to nasal polyps. Many of the earliest observations are now of doubtful value since no clear-cut distinction was made between agonal clots, various tumor masses and true thrombi occurring on the endocardial surface of the heart.

In 1809 Allan Burns¹ clearly described polyps or thrombi of the heart and supported the validity of the existence of such polyps. He noted the presence of such a polyp in the heart of a sufferer of angina pectoris. In 1814 William Wood² made the first observation of a loose thrombus (ball thrombus) in the left auricle in a case of mitral stenosis. In 1872 Zahn³ produced a thrombus mass by injury to vessel walls and by placing a foreign body into the circulation. Later, Eberth and Schimmelbush⁴ observed the early formation of a thrombus under the microscope in the living mesenteric vessel of a dog. As far as can be determined, thrombi have never been produced experimentally in the heart without first causing cardiac infarction. In 1909 Welch⁵ wrote an extensive paper on thrombosis, including thrombi of the heart. He discussed the structure, formation and etiology of thrombi.

A study was made of all the necropsy protocols at the Peter Bent Brigham Hospital for the interval 1913 to 1929 in which 2091 records were reviewed. The incidence of thrombi of the heart in patients coming to necropsy was found to be approximately 5.3 per cent, or 111 instances in 2091 necropsies. The general distribution during these sixteen years was fairly constant with a tendency for the

proportion to increase latterly because of the larger number of patients admitted who were suffering from extreme cardiovascular disease.

Considering the sex incidence of these cases, 73 occurred in males and 38 in females. Thus, the frequency appears to be about twice as great in males as in females. As will be seen below, this probably is caused by the greater frequency of coronary artery disease in the males. It is apparent from Table I that thrombi occurred with greatest frequency in the later years of life. The two decades from fifty to sixty-nine included more than half of all the cases.

TABLE I.

Decades.	No. cases.	Per cent.
10 to 19	1	1.8
20 to 29	1	
30 to 39	16	14.4
40 to 49	20	18.0
50 to 59	32	28.8
60 to 69	32	28.8
70 to 79	9	8.1

In 100 cases in which the Wassermann test was recorded, 89 per cent were negative, 10 per cent ++ and 1 per cent +. This is about the average incidence of a positive Wassermann in all cases coming to the hospital and, therefore, cannot be regarded as significant.

A study of Table II throws light on some interesting relations concerning the sites of thrombus formation. In this series the frequency of thrombi was slightly greater in the auricles than in the ventricles. The two most common sites of thrombus formation were the tip of the left ventricle and the right auricular appendix. This was true for both isolated and multiple thrombi. Thrombi were found to be slightly more frequent on the left side of the heart than on the right (87 to 72). In analyzing the condition in the auricles and the ventricles separately, however, there was a great predominance in the right auricle as compared to the left (60 to 28) and in the left ventricle as compared to the right (59 to 12).

TABLE II.

Location.	No. cases.
Left ventricle alone	31
Right ventricle alone	4
Left auricle alone	6
Right auricle alone	28
Right auricle and left ventricle	11
Right auricle and left auricle	11
Right ventricle and left ventricle	5
Left auricle and right ventricle	2
Left auricle and left ventricle	2
Right auricle, left auricle and left ventricle	5
Right auricle, left ventricle and right ventricle	4
Right auricle, left auricle and right ventricle	1
Left auricle, left ventricle and right ventricle	1

It is apparent from a study of the pathologic finding in these cases that the sequence of coronary artery disease, cardiac infarction and mural thrombosis of the ventricles is the most common mechanism of the production of thrombi in the chambers of the heart.

The weights of the hearts were recorded in 103 cases and are indicated in Table III. From the table it will be seen that in about 92 per cent of the hearts the weights were considerably greater than normal, that is, over 400 gm.

TABLE III.

Weight of heart, gm.	No. cases.	Per cent.
200 to 300	3	2.9
300 to 400	6	5.8
400 to 500	19	18.4
500 to 600	36	35.0
600 to 700	24	23.3
700 to 800	8	7.8
800 to 900	6	5.8
900 to 1000	1	0.9

There were several types of anatomic conditions of the heart associated with thrombus formation. The majority had more or less generalized vascular disease of one form or another with myocardial degeneration; the next large group had valvular disease; there were 8 instances of syphilitic aortitis and 5 cases of rheumatic pericarditis. Of the valvular cases all 18 had mitral stenosis, 5 had aortic stenosis as well, 3 had tricuspid stenosis and 2 had, in addition, both aortic and tricuspid stenosis.

TABLE IV.

Location of infarct.	Incidence.
Pulmonary infarcts	47
Renal infarcts	18
Splenic infarcts	12
Cerebral infarcts*	3
Thrombosis of peripheral vessels.	Incidence.
Femoral artery	2
Left internal iliac artery	1
Superior mesenteric artery	2
Middle cerebral artery	1

* Because in some instances the autopsy did not include the examination of the brain, this figure is probably lower than is actually the case.

The incidence of secondary peripheral emboli and infarction from these thrombi was studied and the results shown in Table IV. The data recorded are explainable on the basis of embolism arising from thrombi located in the proper side of the heart. Cases were not recorded where thrombi occurred in the right side of the heart and infarction took place in the peripheral vessels or organs other than the lungs. It is not possible to conclude that all the recorded infarctions were caused by emboli from crumbling, friable thrombi,

since in some instances the etiology may have been extensive local atheroma of the vessel walls. In the pulmonary group the infarctions of the lung may well have been caused by local changes in the pulmonary vessels, resulting in stasis and infarction. The relative percentage of each mechanism of thrombosis and infarction is difficult to decide.

Of the 34 cases of single auricular thrombi, 19 had embolic phenomena, or 56 per cent. Of the 35 cases of single ventricular thrombi, 15 showed emboli, or 43 per cent. In other words, auricular thrombi were slightly more apt to produce peripheral emboli. Of 32 cases of single thrombi on the right side of the heart, 19 had embolic phenomena, or 59 per cent. Of the 37 cases of single thrombi on the left side of the heart, 15 showed emboli, or 40 per cent. It seems that no matter where the thrombus may be, whether ventricle or auricle, left or right side, the likelihood of resulting emboli is about 33 to 50 per cent.

The general complaints that these patients presented were those commonly associated with cardiovascular-renal problems. Physical examination of the heart showed the usual findings that occur in valvular or myocardial disease. In 85 of the 111 cases there was a definite increase in precordial dullness as determined by percussion. Auscultation revealed murmurs in general accord with the valvular lesions. In 32 cases no murmurs of any character were noted. Poor quality of the heart sounds were recorded in 13 instances, gallop rhythm was present in 11 cases, and systolic murmurs at the apex occurred in 64. An electrocardiographic study was made in 87 cases of this series. Of the irregularities found, heart block of various degrees formed the largest group (32), auricular fibrillation was present in 30 instances and premature ventricular beats occurred in 20 cases. Paroxysmal tachycardia was rare. Sixteen cases showed an abnormal form of the ventricular complex in the electrocardiograms. A study of the kidney function in some showed the usual findings associated with severe cardiovascular-renal disease. Blood pressure studies were unsatisfactory, since many of the patients were under observation a relatively short period of time. Approximately 50 per cent had an elevated blood pressure.

Special Groups of Selected Cases. (a) *Cardiac Infarction with Thrombi.* There were 37 with cardiac infarction in the entire group; of these, 27 were males and 10 were females. Thus in this group males were nearly three times as frequent as females, while in the unselected group males were not quite twice as frequent as females. The average age for females was 62.3 years, for males 59.5 years and the combined average was 60.3 years. There was only 1 case of valvular disease and that showed healed endocarditis of the aortic valve. The coronary arteries were all diseased except three which were recorded as normal. This group included the 22 cases of complete occlusion of the coronary arteries. The site of single

thrombus formation was 22 in the left ventricle, 1 in the right ventricle and 1 in the right auricle. The location of multiple thrombosis was 4 in the left and right ventricles; 6 in the right auricle and left ventricle; 2 in the right auricle, left ventricle and right ventricle; 1 in the right and left auricle and left ventricle. It will be seen from these data that in coronary thrombosis and cardiac infarction thrombi form chiefly in the ventricles and predominately on the left side of the heart. In this series there were only 9 instances of right auricular and 1 case of left and right auricular thrombosis. Ventricular thrombi were present in all the cases.

(b) *Chronic Valvular Disease.* There were 18 cases in this group. Eleven were females and 7 males. The average age of the females was 45.9 years, and for the males 38.1 years. The average age for the entire group was 42.8 years. In this series, as in the preceding group, the females outlived the males. The males have a high incidence of coronary artery disease and a low incidence of valvular disease while the females have a greater frequency of valvular disease and a low rate of coronary artery disease.

In the unselected group thrombi were almost five times as frequent in the right auricle as in the left. In the group (8 cases) of uncomplicated mitral stenosis thrombi were found four times in the left auricle, twice in the right auricle and twice in both the right and left auricle. Thus it would appear that mitral stenosis increased the frequency of left auricular thrombosis. In the 5 cases of mitral and aortic stenosis thrombosis occurred 5 times in the right auricle, twice in the left auricle and once in the right ventricle. In 3 instances of mitral and tricuspid stenosis the thrombi occurred in the right auricle in all cases. In 2 cases of mitral, aortic and tricuspid stenosis thrombus formation occurred once in each auricle. Considering the 18 cases as a whole, there is some slight evidence that valvular disease may effect the location of thrombi. This is especially true of pure mitral stenosis cases. In this entire series it is interesting to note that ventricular thrombosis occurred only once and that was on the right side.

A comparative study of the frequency of pulmonary and peripheral emboli was made for valvular cases and coronary artery cases having complete occlusion of one or more branches of the arteries. Of the 18 valvular cases 17 had associated pulmonary infarcts and only 6 peripheral infarcts. In the 22 cases of coronary artery disease with cardiac infarction and formation of thrombi, pulmonary infarction occurred in 5 instances while peripheral infarction occurred 13 times. Thus coronary artery disease with mural thrombi is associated with a higher frequency of peripheral embolic phenomena into the general circulation while valvular disease is more likely to be associated with pulmonary infarction.

(c) *Auricular Fibrillation with Thrombi.* In 31 cases there was good clinical evidence of persistent auricular fibrillation. This

group was selected in order to study the effect of this irregularity on the site of formation of cardiac mural thrombi. Thrombi were found in the right auricle in 10 instances and in the left auricle in 5 cases. There were 8 cases in which thrombi occurred in both the right and left auricles; 3 cases with thrombi in the right auricle, left auricle and left ventricle; 1 case with left auricular and right ventricular thrombosis; 1 case with right auricular, left auricular and right ventricular thrombosis. There were 3 cases with single thrombi in the left ventricle. Two of these were accounted for by the fact that they were instances in which auricular fibrillation developed after coronary thrombosis. The third case had an infarct probably caused by coronary disease, although the actual condition of the coronary arteries was not recorded in this instance. There were 5 other cases in which ventricular thrombi occurred together with auricular thrombi. There was no gross disease of the coronary arteries sufficient to account for the ventricular thrombi. In this series thrombi occurred in the right auricle in 22 instances, 18 in the left auricle, 6 in the left ventricle and 2 in the right ventricle. Thrombi occurred in the auricles 40 times as against 8 times in the ventricles. Right auricular thrombi were more frequent than left auricular thrombi (22 to 18), while left ventricular were more common than right ventricular thrombi (6 to 2). Fifteen of the 31 cases in this series had chronic valvular endocarditis.

It follows from the above that of the 31 cases who had auricular fibrillation, all but 3 had auricular thrombi (90 per cent). Of the other 80 cases in this entire series that did not show auricular fibrillation only 43 had auricular thrombi (54 per cent). There can be no doubt but that auricular fibrillation increases the incidence of thrombus formation within the auricles.

(d) *Ball Thrombi*. In this series of cases there were 2 instances of ball thrombi. Both cases presented the usual finding reported by Goljajew⁶ in that they occurred in the left auricle in cases of mitral stenosis.

(e) *Heterogeneous Group*. There were 39 cases which did not fall into any large well-defined group. Analysis did not reveal any significant facts.

Mechanisms of the Formation of Cardiac Mural Thrombi. (a) *Coronary vascular disease with occlusion or thrombosis of the lumen* generally results in myocardial infarction. Wearn⁷ has shown that if the process of obliteration of the coronary arteries is slow the vessels of Thebesius gradually may become able to supply to some degree the needs of the heart muscle, and gross infarction may not occur or at least may be less extensive. When the infarcted myocardium involves the endocardium there is probably a liberation of tissue juices which enhances the formation of a mural thrombus. This mechanism accounts for one-third the total number of cardiac mural thrombi.

(b) A second method of formation seems to depend mainly on stagnation of blood in the auricles. Several factors probably play a part in bringing about the final result. Certainly such a functional irregularity as auricular fibrillation effects profoundly the normal flow of blood from the auricle to the ventricle. This combined incoördination of the auricles and the ventricles and the lack of an effective auricular contraction tend to cause stasis in the recesses of the auricle. Disease of the myocardium as caused by rheumatic fever and syphilitic infection may weaken the strength of contraction as evidenced by the replacement of muscle with fibrous tissue. Stenosis of the valves with associated regurgitation slows the flow of blood, increases the work of the heart and favors stagnation of blood in the auricles. Moreover, dilatation of the auricles so common in congestive heart failure adds to the other harmful factors in producing stagnation of blood and in impairing the health of the myocardium and especially of the underlying endocardium. The fact that over 75 per cent of auricular thrombi in this series occurred in the auricular appendices emphasizes the importance of stagnation of blood as a factor in the formation of mural thrombi.

Diagnosis of Cardiac Mural Thrombi. The antemortem diagnosis of cardiac mural thrombosis offers many difficulties. There has never been reported any sign or group of signs that are pathognomonic. Although the finding of cardiac thrombi is not uncommon at necropsy, it is still a rare clinical diagnosis. This is accounted for by the fact that they so frequently remain silent throughout the course of the disease and then form only an incidental postmortem finding. There are certain cases when a thrombus may be suspected. Cases of coronary thrombosis with evidence of peripheral embolism will be found to have a high incidence of cardiac mural thrombosis. Chronic valvular heart disease with auricular fibrillation and evidence of either pulmonary or peripheral infarction will almost surely have cardiac thrombi. Necropsy shows that approximately 20 per cent of hearts with chronic valvular disease and 84 per cent with coronary thrombosis have cardiac mural thrombi. Consideration must be given to the type of case, age limits and presence of other constitutional disease. There will be left a large group in which the thrombi remain silent and give no evidence of their presence and are only to be found at necropsy.

Summary. 1. Uninfected antemortem mural thrombi of the heart were found in 5.3 per cent of all necropsies performed at the Peter Bent Brigham Hospital.

2. Cardiac mural thrombi were twice as frequent in males as in females. The majority of these patients died between the ages of forty to seventy years. The cases with ventricular thrombi following cardiac infarction formed the oldest age group (sixty-two years). There was a large middle-aged group with valvular disease (forty-five years).

3. The frequency of sites of formation of single mural thrombi were: left ventricle, 31; right auricle, 28; left auricle, 6; right ventricle, 4. There were 42 cases of multiple thrombosis. The apices of the ventricles and the auricular appendages were the most frequent sites of formation for mural thrombi.
4. Secondary infarction outside the heart as a result of emboli occurred with the following frequency: pulmonary, 47; renal, 18; splenic, 12; cerebral, 3 (the brain was examined in only a limited number of instances). There were 6 instances of peripheral arterial thrombosis that may have been embolic.
5. Auricular fibrillation definitely increases the incidence of auricular thrombosis.
6. The two most frequent mechanisms for the formation of cardiac mural thrombi are the myocardial degeneration associated with coronary arterial disease and the improper functioning of the auricles leading to blood stasis.
7. The diagnosis of cardiac mural thrombosis presents difficulties, but should be suspected in cases of coronary thrombosis and chronic valvular disease showing evidence of emboli.

NOTE.—We wish to acknowledge the aid rendered by the pathologic department of the Peter Bent Brigham Hospital in furnishing the data.

REFERENCES.

1. Burns, Allan: Observations on Formation of Polypi of the Heart, Diseases of the Heart, 1809.
2. Wood, William: Communication to Edinburgh Med. and Surg. J., 1814, 10, 50.
3. Zahn: Untersuchungen über Thrombose, Virchow's Arch., 1875, 62, 81.
4. Eberth and Schimmelbush: Die Thrombose nach Versuchen u. Leichenbefunden, Stuttgart, 1888.
5. Welch, W. H.: Thrombosis, Albutt's System of Medicine, 1909, pp. 691-821.
6. Goljajew, A. W.: Ball Thrombi of the Heart, Frankfurter Ztschr. f. Pathol., Munich, 1927, 35, 409.
7. Wearn, J. T.: The rôle of the Thebesian Vessels in the Circulation of the Heart, J. Exp. Med., 1928, 47, 293.

FLARIMETER TESTS OF CIRCULATORY FITNESS.

A PRELIMINARY REPORT.

By L. F. MACKENZIE, M.D., P. V. WELLS, D.Sc.,
E. G. DEWIS, M.D., AND L. S. YLVISAKER, M.D.,
NEWARK, N. J.

(From the Medical Department of The Prudential Life Insurance Company of America.)

ABOUT two and a half years ago, stimulated by the painstaking work of H. M. Frost,¹ of the New England Mutual Life Insurance Company, and feeling the urge for some test which seemed to us

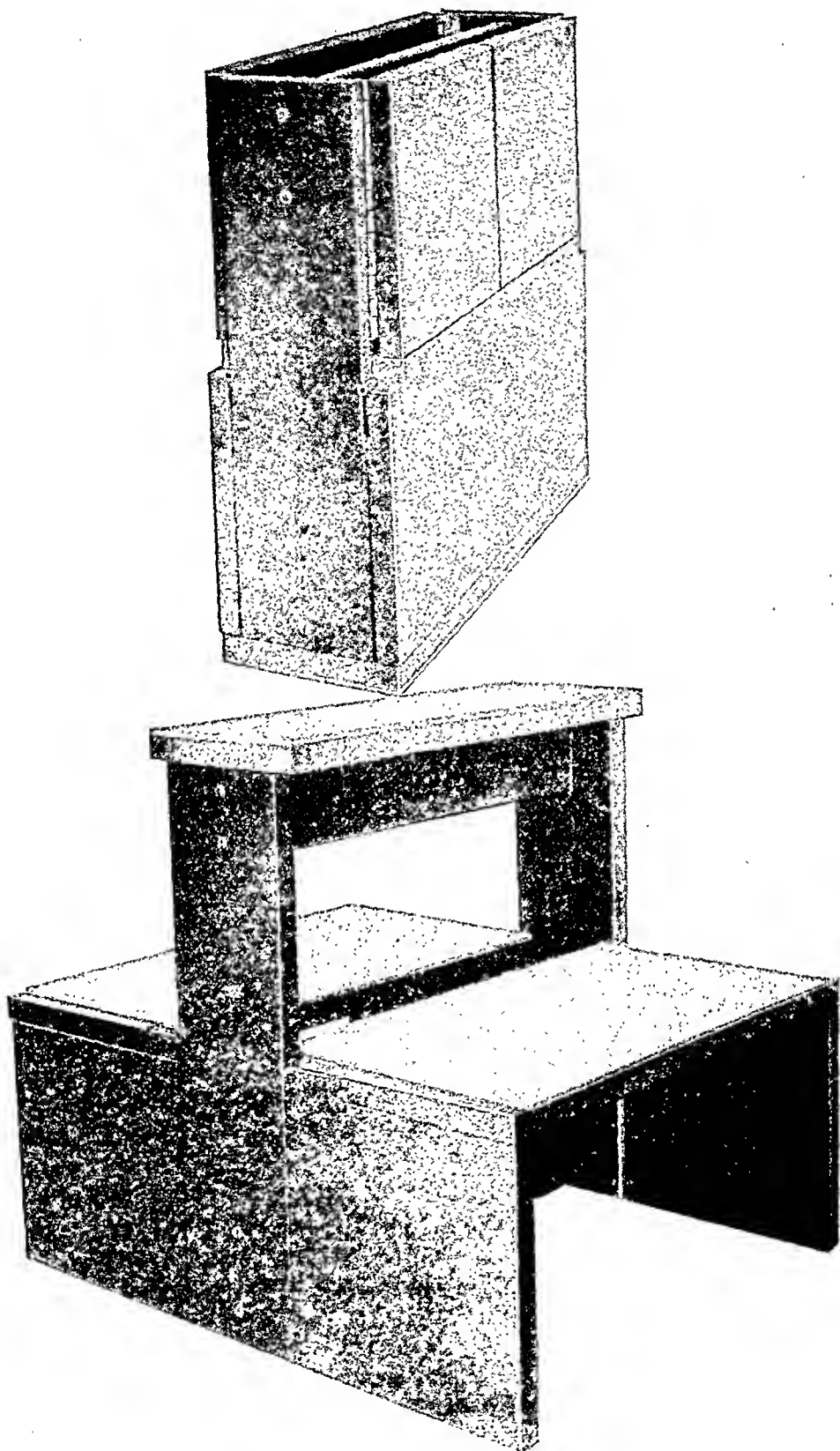


FIG. 1

more satisfactory than those in use, we began investigating our reactions to changes in intrathoracic pressure as revealed by variations in systolic, later in diastolic pressure, and then in heart rate counted at the apex. Our experiences and review of the literature soon convinced us that accurate standardization was essential if comparable results were to be obtained. We wish to emphasize the importance of this, as doubtless lack of it has led to statements by many cardiologists that these tests are of little value in determining myocardial efficiency. We are convinced that the fault was more with the method than the tests. There being no reliable basis for comparison, as no constant standard had been used, results obtained could scarcely be satisfactory.

Within the past year Master and Oppenheimer² have brought forward an exercise test which has made standardization possible, for when carefully applied it permits accurate measurement of work done. It will not be described here because it has been so ably presented by them. They provided tentative standard tables showing the work which should be performed by normals of a given sex, age and weight; the pulse and blood pressure to return to the pre-exercise figures within two minutes. We have simplified these tables for our use by expressing the work done in terms of numbers of ascents, thus avoiding the necessity of calculation and correction for height. The steps described by them have been so modified by us that they are now portable and may be quickly opened and folded together (Fig. 1). A simple, convenient and well-standardized exercise, to which all are accustomed, is now available and comparable quantitative measures of myocardial condition under ordinary methods of examination made possible. As data accumulate and are analyzed, greater accuracy in application and interpretation will be attained by splitting up the present age and weight groupings and adjusting the number of ascents for each group.

We are at present using pulse rather than systolic pressure as a measure of the rate of return to pre-exercise values. Records of both are being kept, however, in the hope that later, through comparison, their relative merits may be established. The importance of shortening of breath developed by this exercise and accurately measured by the flarimeter will be explained later. This shortening, moreover, with rate of its return, gives promise of being a better index of circulatory response to standard exercise than either pulse rate or systolic pressure.

The series of events which occur during the exercise are distinctly different from those which take place when instruments are used to throw strain on the heart through changes in respiration and intrathoracic pressure. The differences between them are tabulated as follows:

Exercise Test.

1. Little change in intrathoracic pressure.
2. Increased respiration with gradual return to normal.
3. No interruption in flow of blood into the right auricle.
4. No diminution in pulmonary circulation.
5. Lactic acid accumulation with oxygen debt.
6. Fatigue.
7. Return of pulse rate to normal delayed in proportion to oxygen debt.

Respiratory Test.

- Pronounced change continuing throughout the blow.
 Increase in respiration only after the test and quick return.
 Marked but temporary interruption of venous return.
 Marked but temporary diminution.
 Slight, if any.
 Fatigue, except of lips, absent.
 Return of pulse rate to normal more rapid.

Respiratory tests will be described under two headings: (1) Vital capacity and (2) breath holding.

Description of Flarimeter. Before discussing these, however, a simple instrument which we designed and which made possible the use of a definitely known intrapulmonary pressure will be described. The instrument developed to its present form, and named the Flarimeter (from "Flare," to blow), is pictured on the next page (Fig. 2). It has enabled us to make observations on the relative values of and comparisons between vital capacity, breath-holding ability, systolic and diastolic blood pressure, heart rate and stroke volume. Briefly described it consists of a glass bottle partly filled with water; the remaining space furnishing an air chamber. The bottle is closed by a tightly fitting rubber stopper having three perforations and capped with a metal plate which serves as a base for three stopcocks and two orifices. Three metal tubes pass downward from the plate through the stopper. One, marked to indicate the required height of water in the bottle, extends to within 2 mm. of the bottom. Its other end, above the plate, is so formed that it contains a stopcock, *B*, over which is a socket, serving when the instrument is in use, to hold a detachable glass manometer tube *A*. This tube is guarded by a valve at the top, to prevent jets of water being blown out, and is in direct connection with the water when the stopcock is open. The second and third tubes pass through the stopper into the air chamber and are also so formed above the plate that each is opened and closed by a stopcock. To one (*C*) is attached a rubber tube of specified length and caliber, at the other end of which is a metal mouthpiece *E*. Through this air is blown into the chamber, forcing the water up the manometer tube to a point distinctly marked at 272 mm. H_2O (20 mm. Hg.) above the level of the water in the bottle. The third tube is so formed above the plate that, by means of a three-way stopcock (*D*) it brings either of two most carefully calibrated orifices into communication with the air chamber. The larger *L* of these permits a flow of 200 cc. of air per second, the smaller *S* of 36 cc. per second at a pressure of 20 mm. Hg. The arm of this stopcock turned to the right connects the large orifice, and to the left the small orifice, with the air chamber. When using the instrument the arms of the three stopcocks must be horizontal and are of such length that the box will not shut while they are in this position. When vertical the three openings into the bottle are tightly closed so that water cannot escape. The orifices are turned downward into the box to prevent any drops of water in the valves from being blown on to the instrument when the blow is begun. The entire instrument is fitted into a walnut-finished wooden case $8\frac{1}{2}$ by 4 by $2\frac{3}{8}$ inches, in which space is provided for the manometer tube, mouthpiece, and rubber tubing.

A very convenient and easily portable instrument capable of accurately measuring vital capacity with the large and breath-holding time with the small orifice is thus provided. It is durable with the exception of the rubber tubing which may be easily replaced. A more complete description is being published in the *Review of Scientific Instruments*.³

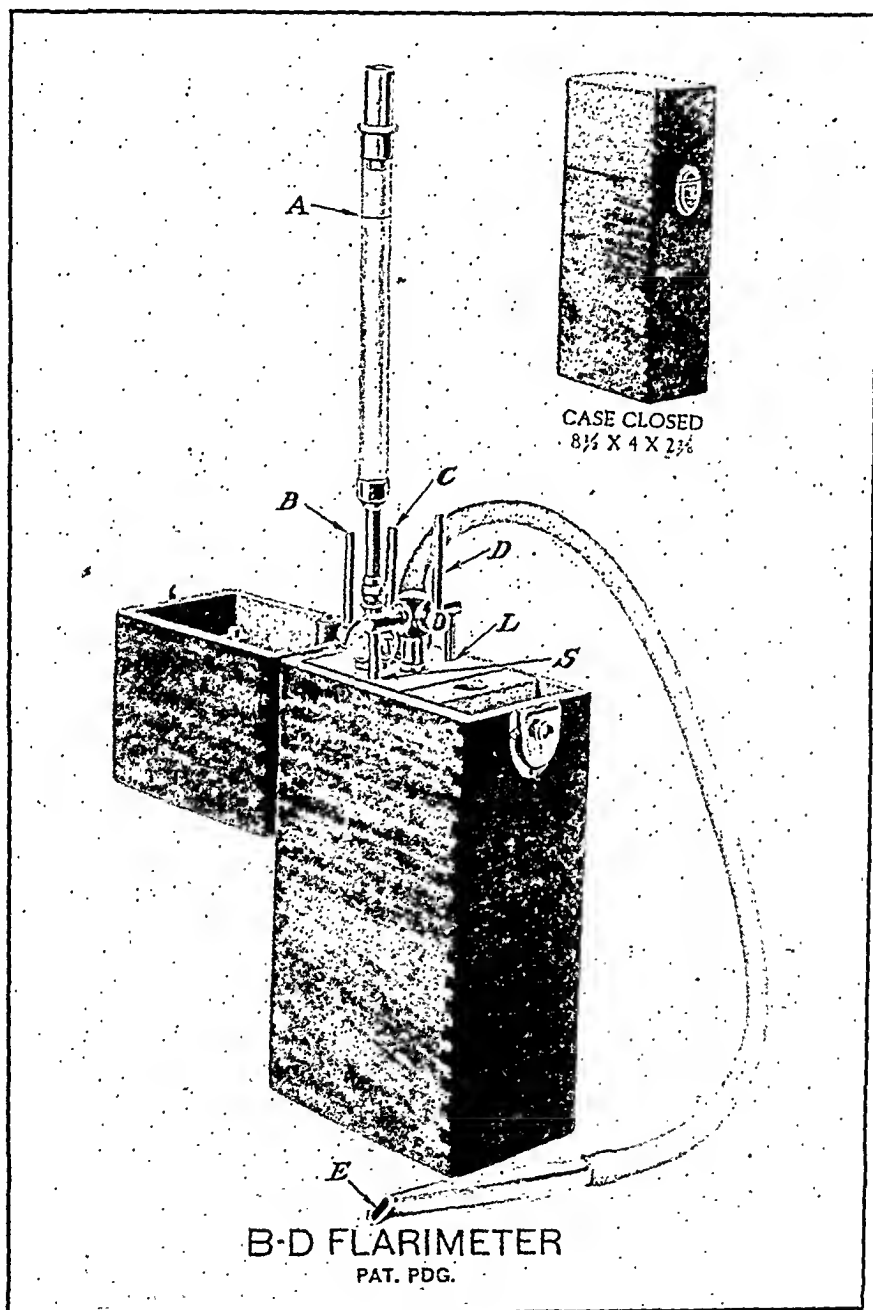


FIG 2

In measuring the vital capacity by the maximum length of blow through the large orifice, the two chief errors are personal to the subject; first, failure to maintain the pressure at the index level throughout the blow;

second, failure to fill the lungs completely before beginning the blow. These errors usually will exceed all the instrumental errors combined. If the examiner is careful, the length of blow can be estimated easily to half a second, which is only 2.5 per cent of a twenty-second blow.

It must be remembered that the pressure drop between mouthpiece and gauge is over 5 mm. Hg. when using the large orifice, so that the length and internal diameter of the rubber tubing are not to be changed. A new piece of the standard tubing should be ordered from the manufacturer* when the rubber deteriorates. With the small orifice, the flow is so small that the intrapulmonary pressure is actually that measured on the gauge.

A water manometer was chosen because it is more sensitive than a mercury and its fluctuations much larger (13.6 times). The psychic effect produced by the larger fluctuations tends to greater accuracy in maintaining the correct pressure. It is always more dependable than is an aneroid.

The accessories necessary are a reliable sphygmomanometer, preferably mercury, a stethoscope with a ribbon arm band to hold the diaphragm over the brachial artery just below the cuff and a watch with a second hand. To obtain sufficient response in systolic pressure, the rate of expiration must be controlled in order to get a cumulative effect. It is only in the later stages of the sustained expiration that the systolic and diastolic pressures rise considerably in normal subjects. If expiration is too rapid or too slow the response is not as pronounced as it is at the optimum rate, which we have found to be about 36 cc. per second when the intrapulmonary pressure is 20 mm. of mercury. This pressure has proved to be the most satisfactory. Heretofore such tests have been made either through large orifices, at many times the optimum rate, or when holding the breath, which is at zero rate of flow. The maximum responses obtained with small orifices are shown by the average values for twenty normal adult males.

TABLE I.—EFFECT OF SIZE OF ORIFICE.

Rate of flow (cc. per second) . . .	0	24	36	48	72
Length of blow (seconds) . . .	69	62	56	51	46
Volume expired (per cent of vital capacity)	0	37	51	62	84
Rise in systolic pressure (mm. Hg.)	16	24	27	25	13

The 36-cc. orifice was chosen because, as indicated by the above table, it produced the best systolic response with the least discomfort; the end of the blow being in the region of tidal breathing (51 per cent of the vital capacity). The individual tested can, therefore, blow more steadily and better control the duration of the physical effort, enabling the examiner to observe the systolic pressure at the end of the blow and the total length of blow with accuracy and ease. All a patient has to learn is to take a full inspiration and blow as long as possible, keeping the water level steady at the index mark. Less force is required to do this with the small orifice than with the large, but this change is learned quickly in a single practice trial.

Hutchinson,⁴ in 1846, began his studies of vital capacity. Since that time it has had its ups and downs in popularity as an evidence of physical condition. In recent years it seems to be again coming into favor. MacLeod⁵ writes: "It has become more and more evident since Peabody and Wentworth's researches, that a determination of vital capacity is of great importance in the diagnosis

* Becton, Dickinson & Co., Rutherford, N. J.

and prognosis of several diseases including heart disease and tuberculosis." Peabody⁶ stated: "The vital capacity of the lungs in heart disease is an index of pulmonary circulation or interference of pulmonary movements on account of circulatory failure."

Whatever one's attitude regarding the possibility of specific interpretation of vital capacity, there can be little doubt that a subnormal value is presumptive evidence of physical impairment and that failure to reach the normal demands explanation. Securing full coöperation by patients is at times a real difficulty. However, the percentage of failures is very small when patience is exercised, combined with instruction and encouragement to do better.

Unanimity of opinion as to the value of this test is lacking among clinicians, many believing that physical examination will disclose an impairment which has progressed to the point where vital capacity has become subnormal and that it is such an individual characteristic that its comparison between persons is not of sufficient significance to make its use really valuable as a routine procedure in the examination of heart and lungs. This attitude will never solve the problem of its worth or convince those who are trying to obtain all possible evidence of physical condition, aids to prognosis and indications of progress under treatment. One fact seems well established, namely, changes in vital capacity in an individual show the progress of many heart and lung impairments.

The spirometers heretofore in use may have had something to do with this attitude, as they were not easily portable. We hope our instrument has overcome this difficulty and that use of the test in home or office is now an easy procedure.

Normally vital capacity is limited by the size of the thorax and flexibility of its walls so that the average values correlate closely with height, weight and surface area. The standard tables by height given by Myers seem to us more practical for general use than is surface area, though the latter gives a slightly closer correlation.

The borderline between normal and subnormal is stated to be 85 per cent by age and height. It is relatively larger in tall persons and in those under the age of forty years. After this age there is a gradual decline, which seems to be less than 1 per cent per year, although the literature indicates the fall is about 1 per cent. We have found that under normal conditions there is no correlation between it and breath-holding ability. The same observation has been made by Jackson and Lees,⁸ who reported a correlation of but 0.16 ± 0.07 in 100 healthy male students. Wittich and Polczak,⁹ on the other hand, found that vital capacity and breath-holding time ran parallel in tuberculosis and cardiorenal disease. Our preliminary studies have led us to the same conclusion, as scatter diagrams have shown the correlation increased with increase in severity of impairments.

Study of the literature, observations in this office and reports

from selected examiners have satisfied us that vital capacity is important, but confirmation of our views will have to await accumulation of data and lapse of time sufficient to give mortality ratios so conclusive that positive statements would be warranted.

Some investigators have believed the vital capacity to be a measure of shortness of breath because it is reduced in many cardiac affections. But a very simple experiment will convince anyone that the length of the flarimeter small orifice blow is a much better measure of shortness of breath than is vital capacity. Immediately after the standard step exercise the small orifice blow is shortened to less than a half of its normal length, while the vital capacity as measured on the Collins is not reduced at all. No change has occurred in the lung capacity. It is the "oxygen debt" in the blood and tissues which has shortened the small orifice blow. Of course, the flarimeter large orifice blow, which ordinarily measures vital capacity, is also reduced in length somewhat under such conditions because the breath-holding time is then a limiting factor.

Turning now to blows with the small orifice, which are really tests of breath-holding ability, we find they give evidence of oxygen depletion, carbon dioxid accumulation and ability of the heart to maintain necessary bloodflow under the strain imposed as a result of the changes in its composition and the increased intrathoracic pressure.

Valsalva's experiment seems to have been the first attempt to determine the effect on pulse rate of increased intrathoracic pressure. Sabrazés,¹¹ in 1902, found breath-holding time following quiet expiration to be about twenty to twenty-five seconds. Stange,¹² in 1914, gave it as forty-five to fifty seconds after maximum inspiration, and found it greatly reduced in pulmonary and cardiac disease. Henderson,¹³ in the same year, pointed out that it was an index of acidosis, and that assuming the sensitiveness of the respiratory center constant the blood stimulus can be ascribed to two factors: (1) CO_2 and (2) other acids (or deficiency in alkali). Whenever the alkaline reserve is low the sensitiveness to CO_2 must be increased, and this we think is his explanation of the shortness of breath. Palcso,¹⁴ in 1928, announced definite shortening in cardiac patients following exercise with marked correlation between this shortening and mortality.

Obviously voluntary apneic pause is a quantitative measure of shortness of breath and can be standardized to replace the qualitative descriptions of the past. The British Royal Air Force have taken as the standard an intrapulmonary pressure of 40 mm. Hg. and require a blow of not less than forty seconds. Bürger,¹⁵ using intrapulmonary pressure of 40 to 50 mm. Hg. with a blow of twenty seconds, produced marked fall in arterial pressure with evidence of partial, or complete, collapse and considered that the blood-pressure reaction shown was an index of myocardial incompetence, as asthenic

hearts were unable to restore the systolic blood pressure to its rest value for over forty seconds. This test seems too severe for general use and quite out of the question in life-insurance examinations, especially as in some of his cases electrocardiographic tracings showed that premature contractions and changes in conduction time had developed.

During the small orifice blow there is first a marked rise in intrathoracic pressure which compresses the great veins and greatly reduces or completely shuts off the blood supply to the right heart. Arterial pressure, therefore, is materially lowered following a brief and sudden rise. These changes are mechanical, and if continued would very soon lead to circulatory standstill with collapse. This does not occur, however, unless the pressure applied is excessive or the individual too weak. Nothing approaching this condition has been observed in our work.

Meanwhile the venous pressure in the cistern of Keith has been mounting and soon exceeds that in the thorax. This is due to increased intraabdominal pressure and vasomotor constriction of the splanchnic vessels squeezing the venous blood into the right heart, and so causing the arterial pressure to rise promptly from its low value. Venous pressure continues increasing to overcome a slowly increasing intrathoracic pressure as air leaves the lungs.

With the initial drop in arterial pressure, coronary and brain circulation are reduced, vasoconstriction of the systemic arterioles intervenes and diastolic pressure rises. Soon interference with aëration depletes the oxygen in the blood and CO₂ accumulates, requiring a steadily increasing bloodflow to compensate for its progressive deterioration. Heart rate, stroke volume, or both, increase, systolic and diastolic pressures mount rapidly and a vicious circle occurs which, if prolonged, leads to severe myocardial fatigue.

To protect the heart, something must stop the blow. The functional ability of the cortical centers (will power) is here largely a matter of oxygen supply. Increased expenditure of energy, in an effort to prolong the blow, combined with oxygen shortage, produce fatigue of these centers with loss of inhibitory control of the basal nuclei. On the other hand, emotional stimuli in nervous individuals may be so great that exaggerated reactions and shortened blows result. This latter is well illustrated in a paper by White,¹⁶ giving results from tests made on soldiers during the World War. The price of apnea produced by this test is a rapidly increasing burden on the myocardium which can be relieved only by loss of voluntary control of the respiratory center.

It is obvious, therefore, that the nervous responses to the flarimeter test are largely characteristic of changes ordinarily taking place in the circulatory system and so intimately involve the heart. If such a load can be thrown on a normal heart, what must be the effect on a myocardium already impaired? Fraser¹⁷ considers that

"the fundamental cause of cardiac dyspnea is inefficiency of the myocardium." If this is admitted, the length of the small orifice blow is a direct measure of myocardial efficiency, when due regard is given to the other factors which may influence shortness of breath in a given case. A diagram of the systolic reaction during a blow is shown in Fig. 3.

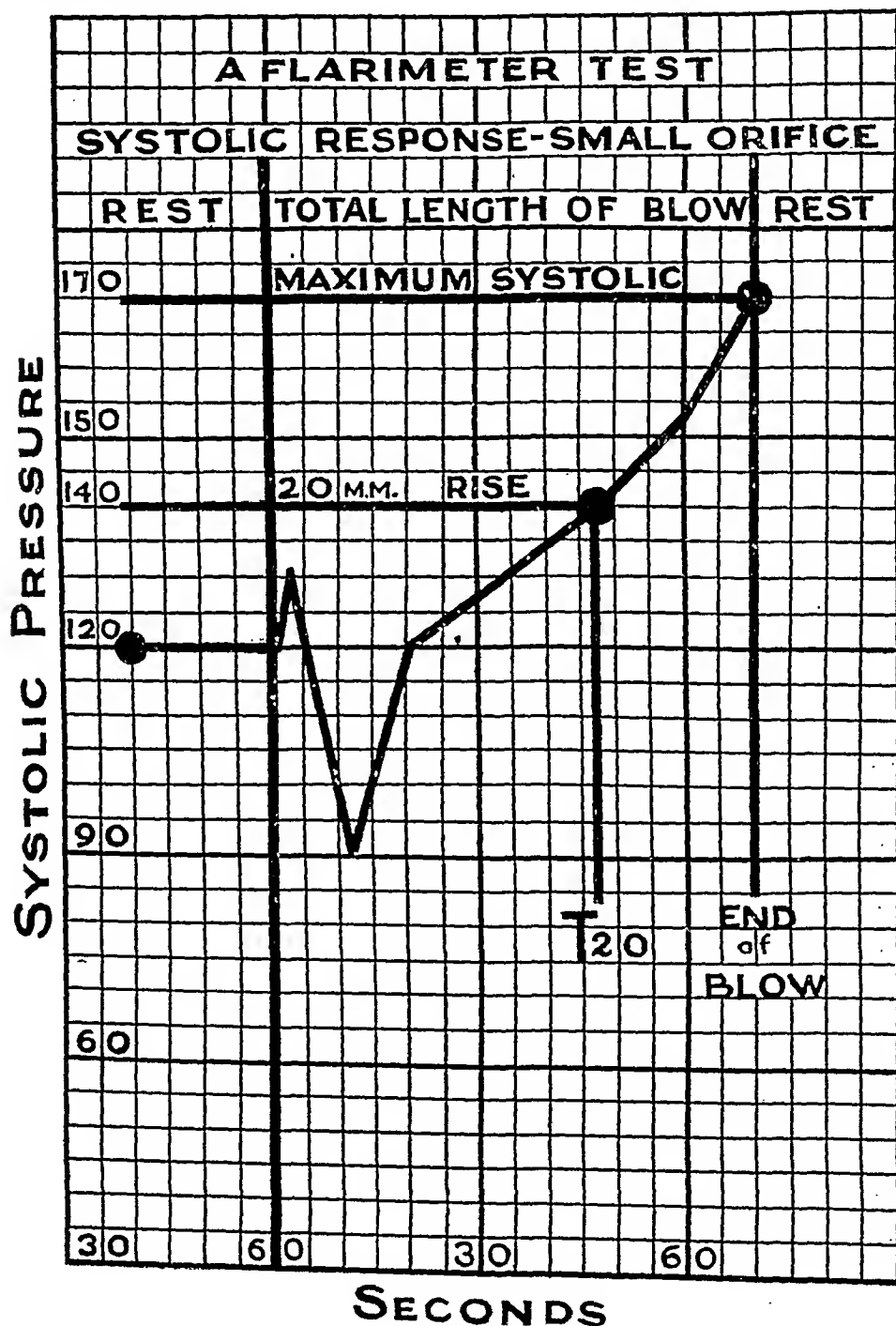


FIG. 3

It will be seen that the responses to the small orifice test are so gradual that it is fairly easy to obtain complete time curves of blood pressure and heart rate during an individual blow. In fact, all the tests in the home office are thus observed, to make sure that nothing is overlooked. So far T20 (the time required for the systolic to rise 20 mm.) seems more significant than the rise taken at the end of the blow, perhaps because it is better standardized. Short T20's suggest myocardial irritability. We use the word "irritability" to imply more than simply one of the properties of heart muscle, and include in it an increased susceptibility to fatigue preceded by hyperactivity of that structure and the nervous mechanisms associated with it. T20 increases with the length of blow, but the latter is not correlated with the systolic rise noted at the end of the blow S+. Yet T20 is negatively correlated with the systolic rise, so that the more irritable subjects (short T20) show a more pronounced S+. A similar index is given by S+ when it exceeds the total length of blow Tm. The latter, Tm (in seconds) should exceed the S+ (in mm.) (Fig. 3).

TABLE II.—FLARIMETER TESTS ON 88 NORMAL ADULT MALES.

Variable.	Ages.	No. of tests.	Median.	Deviation.	Quartiles.		Range.	
					Upper.	Lower.	High.	Low.
Age (years)	18-62	88	30	11.0	43	22	62	18
	18-28	41	22	2.22	24	21	28	18
Per cent of normal weight	18-62	88	99	7.7	104	90	123	73
	18-28	41	98	6.3	103	89	113	80
Per cent of normal vital capacity	18-62	246	100	8.8	106	90	122	76
	18-28	120	101	7.3	108	94	119	80
Excess blood pressure:								
Systolic (mm. Hg.)	18-62	528	-4	9.3	6	-10	24	-30
	18-28	246	1	9.2	8	-8	22	-22
Diastolic (mm. Hg.)	18-62	264	-5	7.5	0	-12	17	-29
	18-28	123	-9	6.6	-1	-15	10	-29
Seconds to rise 20 mm. (T20)	18-62	82	45	9.1	54	37	83	20
	18-28	39	44	8.5	53	36	63	23
Systolic rise (S+)	18-62	85	40	11.4	49	30	74	10
	18-28	39	40	11.3	48	30	74	20
Length of blow (Tm)	18-62	199	54	10.8	62	43	91	21
	18-28	95	47	10.3	58	39	91	31

Flarimeter tests on 88 normal adult males are summarized in Table II. The values for 41 of the subjects (including 22 athletes, under thirty years of age, are given below those for all ages, to indicate the age effects. The groups are normal in weight and vital capacity. In blood pressure they are slightly under the Prudential 1922 experience,¹⁸ probably because less time was given in the field for the nervous factor to subside. Heart and urine examinations

revealed no significant impairments. The smallest variability in the flarimeter responses is in vital capacity, which gives an average deviation of single subjects from the median of about 9 per cent. The corresponding variabilities of T20 and Tm (the length of blow) are 20 per cent, and of the final rise (S+) 28 per cent of the respective median responses.

The upper and lower quartiles indicate the limits within which one-half the cases fall, so that the odds are against a normal response falling outside these limits.

The flarimeter tests are now being applied by selected examiners in the field and clinical cases are being studied. Preliminary results indicate marked reductions in vital capacity, length of small orifice blow and T20 in the more advanced clinical cases. There is positive correlation between these three quantities in the rated and rejected cases, but none among the standard risks.

Tentative normal limits are set up in Table III. To show the severity of the limits, the proportion of the 88 normals called subnormal by each limit is given in the last column. Thus, since

TABLE III.—TENTATIVE LIMITS FOR INTERPRETATION.

Variable.	Symbol.	Subnormal.	Normal.	Normals excluded by limit.
Vital capacity	V	Under 85 per cent	Over 90 per cent	2 per cent
Time for systolic to rise 20 mm.	T20	" 25 seconds	" 35 seconds	6 "
Final systolic rise. . . .	S+	" 20 mm.	" 30 mm.	5 "
Length of blow	Tm	" 40 seconds	" 45 seconds	5 "
Difference (Tm - S+)	" 0	" 10	6 "

only 2 per cent of the normals have vital capacities below 85 per cent of the standard of Myers (by height, corrected for age by adding 1 per cent for each year over forty), the chance is only one in fifty that a normal will be called subnormal by this limit. The chance is one in twenty (5 per cent) for length of blow, and similarly for the other responses. These limits will serve until further data furnish a more reliable basis for interpretation.

The form we are using to record the data obtained is shown on Table IV. It will be seen that a time schedule is required in Tests 3, 4, and 5. This seems to us very important. The stated "maximum systolic" applies to the height to which the systolic pressure has risen when the blow ceases. Frequently following a momentary drop there is a further systolic rise. We are studying this in an attempt to determine its significance. It does not occur in all cases.

TABLE IV.—SYNOPSIS OF TECHNIQUE FOR FLANMIETER TESTS.

Test I	Test III	Test V
Pulse Rate	Seconds	Seconds
Systolic Pressure	25-45 Systolic Pressure	30-45 Pulse Rate
Diastolic Pressure (4th point)	55-60 "Inspire!"	20-60 } Standard exercise for 90 seconds
	60 "Blow!"	60-50 } See table for number of ascents
Test II	Inflate—T20 in seconds	Record number of ascents
Vital Capacity	Maximum Systolic	
	Total Length of Blow	(If no steps are available, use 30 bending movements in 1 minute)
Seconds $\times 0.2 =$ Liters	Test IV	55-60 "Inspire!"
	30-45 Pulse Rate	60 "Blow!"
	30-60 Systolic and Diastolic	Record length of blow
	Record	45-60 Pulse Rate (per min.)—Record
		45-60 Pulse Rate (per min.)—Record

RECORD OF TESTS

Name										Age.....										Sex.....										Occupation.....										Ht.....ft.....										ins. Wt.....									
I.		II.		III.						IV.		V.																																															
At rest		Vital capacity Sec.		Blows with Small Orifice						At rest		Exercise Small Orifice Blow																																															
Pulse Rate		1				1		2		3		Rate		Pulse Rate before																																													
Systolic		2										Systolic		No. Ascents																																													
Diastolic		3										Diastolic		No. Bendings																																													
														Length of blow, sec.																																													
														Pulse Rate end 1 min.																																													
														Pulse Rate end 2 min.																																													
This line for Home Office use only		% of Normal																																																									

Much has necessarily been left out of this article that we would have liked to include; a full discussion of the test will be found in our paper¹⁰ to which we have previously referred. In a pamphlet recently written for our examiners are included "Percentages of Normal Vital Capacity by Height," standard number of ascents for use with the steps, detailed instructions for application of the tests and records of tests on 4 cases with our interpretation of them. We will gladly send a copy of this pamphlet to anyone sufficiently interested to ask us for it.

Summary. *It is claimed:* 1. That accurate standardization of exercise and respiratory tests are essential if comparable results are to be obtained.

2. That the effect produced by exercise is distinctly different from that due to breath holding.

3. That the instrument here described furnishes an easily portable spirometer combined with an orifice for measuring breath-holding ability at a pressure of 20 mm. Hg. and an optimum rate of flow of 36 cc. per second. Standardization of breath holding is thus effected.

4. That throughout the blow the changes in systolic pressure may be noted and evidence of the heart's response easily obtained.

5. That shortening of the blow immediately following the two-step exercise of Master and Oppenheimer, also standardized, and its rate of return are outstanding indications of circulatory fitness.

6. That vital capacity is an important index, but that the length of the small orifice blow with the systolic changes occurring during the blow and their relationships to each other are of more diagnostic and prognostic value.

7. Changes in the systolic curve during a blow are shown, probable reasons for these changes briefly referred to, a table of values presented, derived from 88 normals and tentative limits adopted between normal and subnormal responses.

BIBLIOGRAPHY.

1. Frost, H. M.: Assn. Life Ins. Med. Dir., 1922, 9, 207; N. E. M. Life Ins. Med., 1926, 1, 136; Assn. Life Ins. Med. Dir., 1927, 14, 183.
2. Master, A. M., and Oppenheimer, E. T.: AM. J. MED. SCI., 1929, 177, 223.
3. Wells, P. V.: Review of Scientific Instruments, 1930, 1, 332, new series.
4. Hutchinson (1846): See Myers: Vital Capacity of the Lungs, Williams & Wilkins, Baltimore, 1925, p. 17.
5. MacLeod, J. J. R.: Physiology and Biochemistry in Modern Medicine, 5th ed., C. V. Mosby Company, St. Louis, 1926.
6. Peabody, F. W.: J. Am. Med. Assn., 1924, 82, 1808.
7. Myers, J. A.: Vital Capacity of the Lungs, Williams & Wilkins, Baltimore, 1925 p. 17.
8. Jackson, E. M., and Lees, H. D.: Am. J. Physiol., 1929, 87, 654.
9. Wittich, F. W., and Polczak, J. A.: Am. Rev. Tuberc., 1926, 13, 54.
10. MacKenzie, L. F., Wells, P. V., Dewis, E. G., and Ylvisaker, L. S.: Proc. 40th Annual Meeting Assn. Life Ins. Med. Dir. of America, 1929, 16, 36.
11. Sabrazés, J.: Gaz. Hebd. Sci. Med., Bordeaux, 1902, 23, 99.

12. Stange, V. A.: *Rusky Vrach.*, Petrograd, 1914, 13, 72; *Abstr. J. Am Med. Assn.*, April 4, 1914, p. 1132.
13. Henderson, Yandell: *J. Am. Med. Assn.*, 1914, 63, 318.
14. Palco, B.: *Ztschr. Kreislaufforschung*, 1928, 20, 457.
15. Bürger, M.: *Klin. Wehnsehr.*, 1926, 5, 777, 825.
16. White, Paul D.: *AM. J. MED. SCI.*, 1920, 159, 966.
17. Fraser, F. R.: *Lancet*, 1927, i, 529, 589, 643.
18. MacKenzie, L. F.: *Proc. Assn. Life Ins. Med. Dir. of America*, 1922-1923, 9, 70.

THE PRODUCTION OF HYPERTROPHIC ARTHRITIS BY INTERFERENCE WITH THE BLOOD SUPPLY.*†‡

BY ARTHUR D. GOLDHAFT, V.M.D.,

LILLIE M. WRIGHT, M.A.,

AND

RALPH PEMBERTON, M.D.,

PHILADELPHIA.

IN a series of previous contributions evidence has been adduced to indicate that interference with the blood supply in the finer vessels constitutes part of the disturbance of physiology resulting in the phenomena of arthritis and the rheumatoid syndrome. The lines of reasoning which led to this conclusion were based upon the following: Studies of the blood gases; the blood count at the periphery; the peripheral surface temperature; direct inspection of the capillaries and study of the rate of removal from the circulating blood of substances ingested by mouth under various experimental conditions involving the circulation in the limbs. These studies have been elsewhere reported in detail.¹⁻⁶ It remained, however, to test further the conclusions reached by means of more direct experimentation.

In 1909 Wollenberg⁷ approached the subject of the induction of arthritis from the anatomic and orthopedic standpoints and conducted a series of experiments upon dogs in which ligation of the blood supply to the patella resulted in overgrowths of it. These observations were also elaborated by Axhausen,⁸ but seem to have remained more or less buried in the literature and to have failed to exercise the influence which they should have commanded. It

* The chemical part of the work here reported is from the Laboratory of Clinical Chemistry, Presbyterian Hospital.

† The work here reported is part of a study on chronic arthritis in collaboration with Dr. Robert B. Osgood, of Boston. The expenses of the investigation were defrayed by contributions from various sources, including a number of patients.

‡ Preliminary reports of this work were made as follows: *J. Michigan Med. Soc.*, 1927, 26, 599; *Arthritis and Rheumatoid Conditions; Their Nature and Treatment*, Philadelphia, Lea & Febiger, 1929.

was decided, therefore, to repeat the experiments of Wollenberg, especially in the light of the present viewpoint, reached by a different line of investigation. Corroboration of Wollenberg's results would obviously go a long way to substantiate the conclusion above outlined.

In attempting the induction of any of the phenomena of arthritis it is important to bear certain facts in mind. Following the classical morphologic studies of Nichols and Richardson,⁹ arthritis has come to be recognized in this country, and essentially also in England under different names, as presenting in general two types, namely, atrophic and hypertrophic. Nichols and Richardson called these types proliferative and degenerative respectively and specifically stressed that, while these types are apparently justified morphologically and clinically, they do not necessarily represent finality in classification, and that they exhibit, avowedly, some points of contact and apparent merger. In general, however, atrophic arthritis represents the variety seen for the most part in persons below mid-life and hypertrophic arthritis that encountered in largest measure at or beyond mid-life. Atrophic arthritis is, furthermore, generally thought to be a frequent expression of the effect of infectious factors and hypertrophic arthritis of physiologic disturbances of a more generic nature, such as those referable to age, trauma, the climacteric and the like. Some students of the subject have dogmatized rather strongly as to the invariably infectious nature of atrophic arthritis and some have denied that infection plays any etiologic rôle in hypertrophic arthritis. It can fairly be said, however, that the evidence is not so complete as to justify such dogmatism. There are undoubtedly many factors, other than infection, operative in at least a contributory sense in the induction of atrophic arthritis; there is strong evidence that at least some, possibly many, cases of hypertrophic arthritis are themselves associated with and conceivably referable to infectious agencies. This statement is believed necessary for the proper interpretation of the experimental results to be described.

The methods used were as follows: Six apparently healthy dogs were selected, of varying ages, temperature, respiration and pulse being normal. They presented no nasal discharge or conjunctivitis and bowel movement and urination were apparently normal. The animals were all given an initial bath in a 5 per cent solution of lysol to remove external parasites and were subsequently bathed in the same way twice a month during the conduction of the experiments. Microscopic examination was made of the feces in all cases for internal parasites. All dogs showed two parasites, namely, ascarides (roundworm) and hookworm. The animals were accordingly starved overnight and given tetrachlorethylene in a capsule, in the dosage of 3 cc. per 22 pounds of weight. Examination was made again in three weeks and found to be negative for ova and

parasites, and this examination was repeated at three-week intervals throughout the experiment. Twenty-four hours prior to operation under ether anesthesia a light meal, consisting of milk only, was given to each dog.

The hair in the region of the patella of the leg to be operated upon was shaved and the skin was scrubbed thoroughly with soap and water for two minutes. The region of the patella was painted with iodine, then ether, then iodine again. A pad of cotton soaked in a 5 per cent solution of lysol was placed at the site of the patella for an hour before operation. Instruments and surgical material were sterilized in the orthodox manner. The dogs were then placed under general ether anesthesia and the ensuing operation was performed, following the method of Wollenberg, with the aim of cutting off the blood supply to the patella of one leg. The other leg was left as a control. A linear longitudinal incision of 2 inches was made directly over the patella through the skin, subcutaneous tissue, and part of the deep fascia. The deep fascia was dissected so as to free the patella and the overlying and surrounding tissues. The following technique was then utilized in tying off all bloodvessels No. 12 twisted silk being employed. At a point beginning at the distal edge of the patella a row of overlapping sutures, one in advance of the other, was carried in a circuitous manner completely around the patella to the point of beginning. A second row of overlapping sutures was placed around the first row of sutures in such a manner that the loops of the second row were half way between the loops of the first row. When each suture was put in place the slack of the previous suture was taken up. The wound was closed and dressed in the usual manner. After the operation the dogs were given no food until they could lap water voluntarily. On the evening of the operation the dogs were given a light meal consisting of a cupful of milk, toast and vegetables. No weight was placed by any of the dogs for ten days on the leg operated upon. For several days there were extreme pain and lameness and also a marked edema. Ten days after the operation the wound had healed by first intention in every instance.

The arterial anastomosis around the knee joint in the human being, according to Gray,¹⁰ is formed by branches from six arteries—the medial, lateral and highest genicular, the fibular, the descending branch of the lateral femoral circumflex and the anterior recurrent tibial arteries. In the dog, according to Dr. William Lentz, professor of anatomy at the Veterinary School of the University of Pennsylvania (personal communication), the patella and the knee joint are supplied by branches from the two anterior femoral arteries, from the articular branch of the anterior femoral artery and from the saphenous artery.

The blood supply to the patella, in this operation, was apparently completely interrupted, at least for a long time. The vessels in the

tissue surrounding the patella were tied off and those from the skin and superficial tissues were dissected away. Considering the fact that interruption of the blood flow was followed by progressive consequences as late as eight months after the operation, it is presumable that the circulation was markedly interfered with, if not entirely obstructed, until the dogs were killed. The period of most graphic and possibly most rapid change was apparently between the third and the sixth months.

An incomplete series of injection experiments suggests that a compensatory circulation may have been established to a very small degree, but this is by no means certain. In any event there can be no question that a radical reduction was achieved in respect to the amount of blood reaching the patella through the normal channels.

In one animal the control leg had been the site of a resection of the tibial nerve three months and three weeks previously, but recovery had been uneventful, complete and without lameness.

Five of the six dogs lived through the period of nine to ten months, during which the experiment lasted. Dog IV ("Brown") died accidentally four months after the blood supply to the patella had been ligated. Brief reference is later made to this animal, but the results of the operation do not justify consideration in the final conclusions.

In considering the effects of an operation of the above nature in, or near to, a joint, the possible effect of trauma of any kind in the production of an arthritis is to be borne in mind. For this reason experiments were carried out on two animals with the aim of eliminating from consideration any mechanical influence arising from the operation, or from sutures introduced, in the production of arthritic changes later to be noted. An amount of No. 12 silk, equal to that used in the ligating experiments, was placed completely around the patella at the same depth as in the experiment previously described. The silk was simply fixed in position and care was exercised to avoid tying off any bloodvessels or interfering with their blood flow. Preparation and operative technique were otherwise as described. The reaction after this operation was similar to that which followed ligation of the patellar vessels.

Protocols. Dog I.—A male, mongrel beagle hound, named "Hound," 30 pounds in weight, two years of age, with completely united epiphyses, was operated upon on January 23, 1927. The blood supply to the patella of the right leg was ligated, resulting in lameness of that leg. Roentgen rays of the leg operated upon, on the following dates, showed:

April 30: Overgrowth of the patella distally, and an indented area proximally.

July 14: A slight increase in the length of the overgrowth.

October 17: Greater increase in calcification of the overgrowth.

On November 24 the dog was sacrificed.

Examination after death showed a normal left leg, but thickening and adhesions of the fascia around the joint capsule of the right leg (the leg operated upon). The patella and sheaths were dissected from the joints and were split lengthwise. The left (normal) patella could be dissected and stripped easily and could be split only with great effort. All of the normal patellæ were easily dissected and stripped, but very difficult to split. The right patella could be dissected and stripped only with difficulty. It showed a distal overgrowth, an irregular rounded extension of the patella, 12 per cent of the length of the normal patella. The patella was discolored on its articular surface and the split surface showed areas of brown-colored tissue.

DOG II.—A female, mongrel dog, named "Wooley," 30 pounds in weight, one year of age, with completely united epiphyses, was subjected to the same operation upon the right leg on January 23, 1927. Roentgen rays of the leg operated upon, on the following dates, showed:

April 30: A slight overgrowth of the patella distally, and a small indented area proximally.

July 14: An increase in the overgrowth and in the calcification of the overgrowth as well as in the area of indentation.

October 17: A greater calcification of the overgrowth.

On October 17 the dog was sacrificed.

Examination after death showed a normal left leg, but thickening and adhesions around the right joint and capsule. The left (normal) patella could be dissected and stripped easily and clearly. It was shiny, smooth and white on its articular surface, as were all normal patellæ. The right patella (the patella operated upon) could be dissected and stripped with great difficulty only. It showed a distal overgrowth, a fully rounded extension of the patella, 53 per cent of the length of the normal patella. The overgrowth was entirely covered with fascia and, on beginning dissection, it was difficult to tell where the overgrowth ended and the tendon sheath began. The nonarticular surface of the patella had several knobby, bony, fragile growths. The articular surface was darker in color than the normal.

DOG III.—A male, mongrel Irish terrier, named "Irish," 25 pounds in weight, one and a half years of age, with completely united epiphyses, was operated upon on May 15, 1927. The blood supply to the patella of the left leg was ligated, resulting in lameness of that leg.

This dog had been subjected to a nerve resection of the right leg on January 23 without any apparent change from the normal as to function. This leg was used as the control.

Roentgen rays of the left leg on the following dates, showed:

July 14: An overgrowth of the patella distally.

October 17: An increase in the overgrowth and in the calcification of the overgrowth, and an indented area proximally.

February 27, 1928: Slight further increase in the overgrowth.

On February 27 the dog was sacrificed.

Examination after death showed an apparently normal right leg and joint, but thickening and adhesion of the fascia around the joint of the left leg (the side of the ligation) with several small injuries on the condyles of the left femur. On observation, the right patella appeared normal, but it could not be dissected as easily as the other two normal patellæ. The left patella (the side of the ligation) could be dissected and stripped with great difficulty only. It showed a distal, spear-head-shaped overgrowth, 50 per cent of the length of the normal patella. The overgrowth was entirely covered with fascia and, on beginning dissection, it was difficult to tell where the overgrowth ended and the tendon sheath began. Its articular surface

was darker in color than that of the normal. Near the proximal end of the articular surface each patella showed a broad, shallow groove which was probably a congenital deformity.

Dog IV.—A male, mongrel beagle hound, named "Brown," 25 pounds in weight, two and a half years of age, with completely united epiphyses, was operated upon as a control on February 5, 1928. In this operation sutures were inserted around the patella of the right leg, but the blood supply was not tied off. Recovery was complete and without lameness. Roentgen rays of the right leg on May 10 and July 12 showed no change from the normal.

On August 1 the blood supply to the patella of the left leg was ligated, resulting in lameness of the leg operated upon. Roentgen rays of the left leg on September 27 and December 13 showed no change from the normal. On December 12 "Brown" died from malnutrition following a severe gastroenteritis, probably due to eating chicken feed composed of meat scraps, bran, middlings and corn meal.

Examination after death showed an apparently normal right leg and joint, but thickening and adhesions of the fascia around the left joint (the side of the ligation), marked injuries to the left femur and a deformed articular surface of the left patella with overgrowth of the articular cartilage centrally. The left patella was 1 cm. nearer the tibia than the right patella. Roentgen rays after partial dissection showed a change in shape of the left patella, but no overgrowth. The right patella could not be dissected or stripped as easily as could the two normal patellæ, because of the slight amount of thickening and adhesions of the surrounding tissues due to the control operation. It could be split without great effort. The left patella (the side of the ligation) could be dissected and stripped only with difficulty and also could be split very easily. It showed no overgrowth, although it did show a change in shape. The articular surface was somewhat shiny and smooth, but darker in color than normal patellæ.

Dog V.—A male, mongrel, beagle hound, named "Yellow," 25 pounds in weight, two and a half years of age, with completely united epiphyses, was operated upon as a control on February 5, 1928. In this operation sutures were inserted around the patella of the right leg, but the blood supply was not tied off. Recovery was complete and without lameness.

Roentgen rays of the right leg on May 10 and July 12 showed no change from the normal.

On August 1 the blood supply to the patella of the left leg was ligated, resulting in lameness of the leg operated upon.

Roentgen rays of the left leg, on the following dates, showed:

September 27: A change in shape, a beginning distal overgrowth, and a fuzzy appearance of the patella.

January 10, 1929: Increased overgrowth of the patella.

April 4: A slight increase in the overgrowth and in the calcification of the overgrowth.

May 17: A slight increase in the length, in the width and in the calcification of the overgrowth.

On January 10 a skin or surface infection of the left leg was noticed, caused apparently by the rubbing of the chain with which the dog was tied. There was no fever, swelling, lameness or pain. No complications developed. The infection healed in ten days under treatment with a 1 per cent solution of chloramin-T (Squibbs' Dakin-Carrel solution).

On May 17 the dog was sacrificed.

Examination after death showed an apparently normal right leg, but much thickening and many adhesions of the fascia around the left joint

(the side of the ligation) and marked erosion of the condyles of the left femur. The right patella appeared normal, although it could not be dissected and stripped as easily as a normal patella, because of the slight amount of thickening and adhesions of the surrounding tissue due to the control operation. Also there were several fragile areas present on the nonarticular surface. The left patella (the side of the ligation) could be easily split, and could be dissected and stripped only with difficulty. It showed a distal overgrowth, a fully rounded extension of the patella, 31 per cent of the length of the normal patella. On beginning dissection it was difficult to tell where the overgrowth ended and the tendon sheath began. The nonarticular surface was knobby. The articular surface was somewhat shiny and smooth.

Dog VI.—A male, mongrel collie dog, named "Collie," 20 pounds in weight, eight months of age, with epiphyses not united, was operated upon on August 14, 1928. The blood supply to the patella of the left leg was ligated, resulting in lameness of the leg operated upon.

Roentgen rays of the leg operated upon, on the following dates, showed:

September 27: A very small overgrowth distally and a small indented area proximally with an increase in the calcification of the patella.

January 10, 1929: A very slight further increase in the overgrowth.

April 4: A very small further increase in the overgrowth.

May 17: No change from the Roentgen ray of April 4.

On May 17 the dog was sacrificed.

Examination after death showed a normal right leg and patella, but thickening and adhesions of the fascia surrounding the left joint, a slight injury on the condyles of the left femur, a deformed articular surface of the left patella and overgrowth centrally of the articular cartilage of the left patella. The left patella could be dissected and stripped with only a slight amount of difficulty, and could be split easily. It showed a distal overgrowth, a rounded extension of the patella, 11 per cent of the length of the normal patella. On beginning dissection it was rather difficult to tell where the overgrowth ended and the tendon sheath began. The patella appeared somewhat smooth and shiny on its articular surface.

The above experiments show clearly that at the end of a period of from nine to ten months definite and considerable overgrowth of the patella had taken place in every dog following interference with the blood supply to that region. In the animals in which non-absorbable suture material in equal amount had been placed around the patella following an otherwise identical operation, no observable overgrowth of the patella took place. There was possibly a slight increase in density at the distal end of the patella of "Yellow," but the contrast between these two sets of animals was beyond all possibility of error. In all dogs, including the controls, in which silk ligature had been placed as a foreign body, there was a certain amount of thickening and adhesion of the structures in the neighborhood of the patella tendon and the joint capsule. This was most marked in the animals in which the blood supply had been interfered with and resembled grossly the arthritic changes observed in human beings in the so-called "periarticular" structures. The most graphic changes in these last-mentioned animals were in connection with the patella, which showed unmistakable overgrowth of marked and

varying degree. The first evidences of this were to be seen upon Roentgen ray examination two to three months after the operation. (The left patella of the dog "Brown," at the time of death, four months after ligating the blood supply to it, showed no overgrowth, but did show a slight change in shape.) In all dogs which lived as long as nine or ten months the overgrowth varied in size from one-ninth to more than one-half that of the original patella itself. Three of the 5 dogs showed overgrowths of 31, 50 and 53 per cent of the size of the normal patellæ. The other 2 dogs showed overgrowths of 11 and 12 per cent of the size of the normal patellæ. "Collie" (Dog VI), the dog that showed the least overgrowth, was very young, being eight months of age at the beginning of the experiment. "Hound" (Dog I), the dog that showed an overgrowth of 12 per cent, was one of the oldest animals. It is interesting to observe that, whereas there was a considerable amount of thickening and adhesion of the associated structures, the overgrowth of the patella was apparently entirely discrete. In the Roentgen ray plates in no instance did it merge more or less gradually into the attached tedinous tissue as one might possibly have expected. Roentgen ray study suggests, in some cases, that the overgrowth of the patella began by means of scattered areas of calcified matter of varying density within the limits of what proved later to be the overgrowth itself. Later, the advancing edge of the new growth of the patella became characterized by what appeared to be a definite line of limitation, almost as though a membrane had enclosed it. On dissection, nine or ten months after the operation, however, this was not so apparent. The shape of the forward projection varied between a pointed spear-head-shaped overgrowth and a fully rounded extension of the patellar bone itself. As growth proceeded, the structure of the overgrowth, light at first, as shown by the Roentgen rays, became denser, obviously due to increasing impregnation with osseous salts.

It is obvious that operative infection might be suspected of contributing to the results achieved. This explanation is unlikely, however, in view of the fact that the dogs showed no evidence of infection locally or systemically or at autopsy. Furthermore, essentially the same technique was used in the control animals which showed none of the changes above described. It is to be noted that, in the appended report on microscopic findings, there was "no sign of acute inflammation or necrosis."

Histologic study of one such typical specimen was kindly made by Dr. Edward Krumbhaar, professor of pathology at the University of Pennsylvania, who reported as follows:

"As compared with the normal patella, the experimental patellæ, cut in longitudinal section, is prolonged at one end to a point of dense tissue visible to the naked eye. Under the microscope this is seen to merge imperceptibly with the true bone. At its distal end it is composed of dense, relatively

acellular, pale pink staining material, with long thin nuclei, many of which lie on the edge of thin narrow slits. As the normal bone is approached, these spaces become more numerous and more oval, with the cell lying more in the lumen, until finally the ordinary bone cell in its space predominates. On the side of the articulation it is bounded by fibrous tissue, which persists until the synovium and cartilage is reached. On the other side the osteoid tissue extends well past the level that is true spongy bone, eventually to merge with its periosteum. The fatty tissue between the bone spicules contains definitely more cells than in the control; that is more lymphocytes, plasma cells and possibly hemopoietic cells, such as neutrophils. There is no sign of acute inflammation or necrosis. **DIAGNOSIS—OSTEOID TRANSFORMATION OF TENDON, BEGINNING MYELOID ACTIVITY?"**

The fundamental processes concerned in the development and overgrowth of bone, physiologic and pathologic, are by no means clearly understood. Importance would be attached to fuller knowledge of the chemical changes taking place in respect to the mineral salts, chiefly calcium and magnesium, and also the phosphorus, in experiments such as the above. Analyses were accordingly undertaken, with the coöperation of Dr. F. A. Cajori, upon the newgrowth, upon the original portion of the patella operated upon and upon the patella of the control side. These analyses included the total ash, calcium, magnesium and phosphorus content. The total ash of the patella tendon sheath was also determined.

The patella was divided longitudinally to provide portions for section and for chemical analysis. The halves for chemical study were further divided into the original patella and the overgrowth. These were then dried at 100° C. to constant weight and ashed in a platinum crucible to a white ash. The ash was weighed, and then dissolved in a small amount of hydrochloric acid and made up to 100 cc. Twenty cubic centimeters were used for analysis. In the case of the ash of the overgrowth, which was dissolved in hydrochloric acid and made up to 50 cc., 10-cc. portions were used for analysis. For calcium and magnesium the method of Kramer and Howland¹¹ was used; for phosphorus, Brigg's¹² method for phosphorus in urine was followed.

Summary of Chemical Studies. The table on page 395 gives the results, all of which are averages of several closely agreeing analyses.

It will be seen that the operation of tying off the patella had little effect on the ash, calcium and phosphorus content of the patella. The percent of magnesium is increased, however, in the ash of the patella of the side operated upon, and especially in the ash of the newgrowth (overgrowth) on that side. This overgrowth is not completely calcified, as evidenced by the fact that the overgrowth has a somewhat lower ash content than have the patellæ.

The ash content of the tendon sheaths on the side operated upon is a little higher than the ash of the tendon sheath on the control side. The small amounts of ash available for weighing after the burning of the tendon sheath and the uncertainty of clean dissection of the tendon sheath before ashing make these results less satisfactory.

	Dog.		
	"Hound."	"Wooley."	"Irish."
Ash, per cent:			
Unoperated	50.87	52.98	54.46
Operated	51.69	52.72	54.74
Overgrowth	44.76	
Calcium, per cent of ash:			
Unoperated	41.27	41.09	40.62
Operated	41.35	40.41	40.32
Overgrowth	41.52	
Phosphorus, per cent of ash:			
Unoperated	17.10	17.65	17.50
Operated	17.97	17.85	17.41
Overgrowth	18.03	
Magnesium, per cent of ash:			
Unoperated	0.54	0.51	0.65
Operated	0.67	0.65	0.66
Overgrowth	0.92	
Tendon sheath, per cent of ash:			
Unoperated	1.75	1.82	0.55
Operated	2.15	2.23	0.53

The above analytical results apply to the first two dogs only. The patellæ of "Irish" (Dog III) do not differ with respect to magnesium. In the ash of both patellæ the per cent of magnesium is high, similar to the magnesium content of the patellæ on the side operated upon of the other two dogs. It should be noted, however, that "Irish," in contrast to the other two, had had a nerve resection on the leg which later served as the control in the experiments on ligating the patellæ.

An increase in the magnesium in bone has been noted by others in abnormal bone conditions. McCrudden¹³ found an actual increase in magnesium in the bones in osteomalacia. Gassman¹⁴ reports finding increased magnesium in rachitic bone, and Toverud¹⁵ found an increase of magnesium in the teeth of Howe's guinea pigs with chronic scurvy.

It may be concluded that the derangement in bone metabolism following the tying off of the circulation to the patella brings about a condition seen also in certain pathologic states affecting bones, in which magnesium is deposited in greater amounts than normally takes place.

Discussion. Taken in conjunction with the work of Wollenberg, these experiments admit of no doubt that at least some of the characteristic bony changes of arthritis can be induced by interference with the blood supply. The type of arthritis which, obviously, is most strongly suggested in these experimental results is hypertrophic arthritis. It would be a mistake, perhaps, to suppose that only hypertrophic manifestations can be brought about by this measure. There are apparently a few areas to be observed in the specimens in which a certain amount of erosion or atrophy suggests the atrophic type. The phenomenon of overgrowth of bone or atrophy of bone is not necessarily the only definitive feature of one or the other kind

of arthritis. Leriche and Policard¹⁶ state that "bone resorption and osteogenesis appear indissolubly linked" and that "it is exceptional to find bone rarefaction without noting in the vicinity a certain degree of new bone formation." Many cases of atrophic arthritis are accompanied by some overgrowth of bone. In other experiments in process of being reported by the writer and his associates the evidence is strong that disturbance of the blood supply in the direction of vasoconstriction is most marked in atrophic arthritis, although well marked also in hypertrophic arthritis.

The subject of morphology of bone which had perhaps reached a rather inactive condition has recently been opened up, partly through the stimulating work of Leriche and Policard. No attempt will be made here to discuss this large field beyond stating that these authors have shown that older conceptions in this connection may require some revision. These workers have reached a conclusion as regards normal bone which is in close rapport with the conclusions reached by the present writer and his associates in relation to arthritis. Thus, Leriche and Policard advance, as a thesis fundamental to an understanding of osteogenesis, the general principle that activity of the circulation tends toward rarefaction of bone, and, conversely, that stasis of the circulation favors ossification. This latter is in striking agreement with the work here reported. Therefore, while the results of the experiments here described resemble closely the phenomena of hypertrophic arthritis, the writers do not mean to indicate that the processes concerned are confined solely to that variety. They believe, indeed, that they may also operate under somewhat different conditions in atrophic arthritis.

The incidence of positive results in the present series was very high. It is entirely conceivable that at the hands of others or at the hands of the present workers in another series, the proportion of positive results might be lower. The main point at issue is, not that the results described will invariably follow the above operative procedure, because the present series is too small to admit of such a conclusion, but that in at least a definite proportion of cases interference with the blood supply is followed by overgrowth of bone.

In describing experiments designed to elucidate the pathologic background productive of arthritis and rheumatoid phenomena, it seems necessary to point out that the changes in physiology observed are not out of consonance with the recognized influence of infection in many cases of arthritis. The belief that all cases of arthritis are due only to infection is so frequently to be met, among those who are not studying the disease intensively, that the necessary link between even a definitely causative infection and the end result, arthritis, is largely overlooked. The most cursory survey of the problem will indicate that there must be a medium, or chain of disturbances, through which such infection, when operative, expresses itself. Accepting the premise that many cases of arthritis are precipitated by infection and that many other factors are opera-



FIG. 1.—Roentgen ray showing the normal patella of dog "Irish." (The shadow behind the patella is the condyle.) The Roentgen ray was taken before the ligation of the patellar vessels.



FIG. 2.—Roentgen ray showing the overgrowth of the patella of dog "Irish," two months after ligation of the patellar vessels.

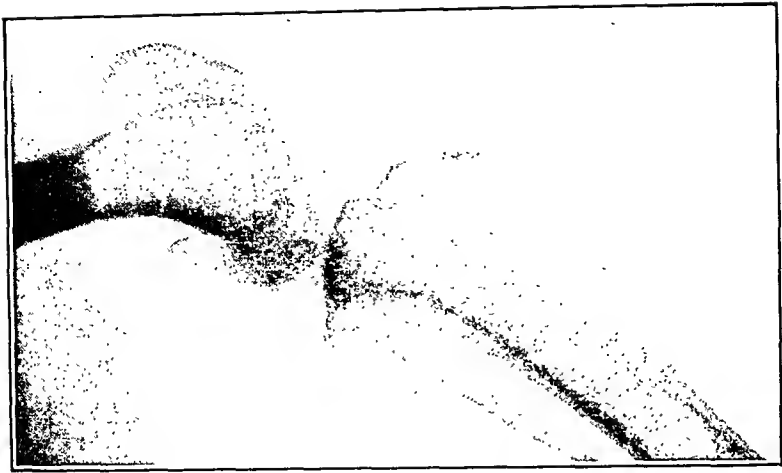


FIG. 3.—Roentgen ray showing the overgrowth of the patella of dog "Irish." Nine and a half months after ligation of the patellar vessels.

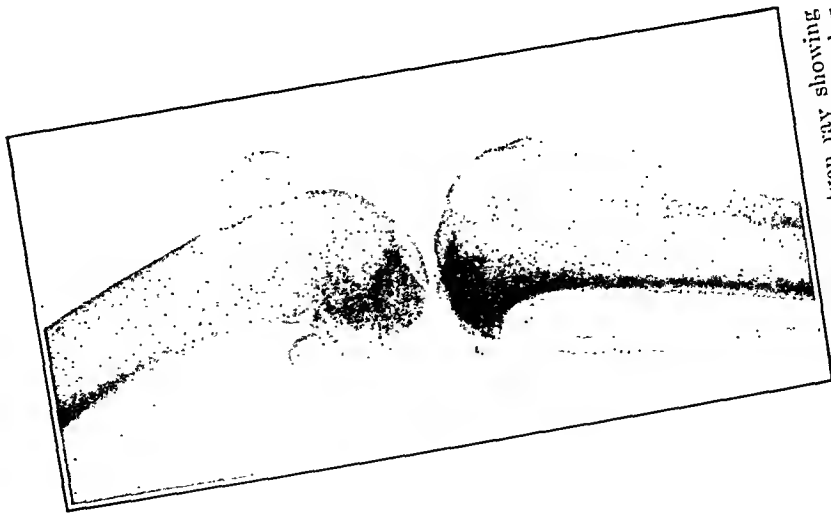


FIG. 4.—Roentgen ray showing the normal patella of the dog "Wooley." (The shadow behind the patella is the condyle.)

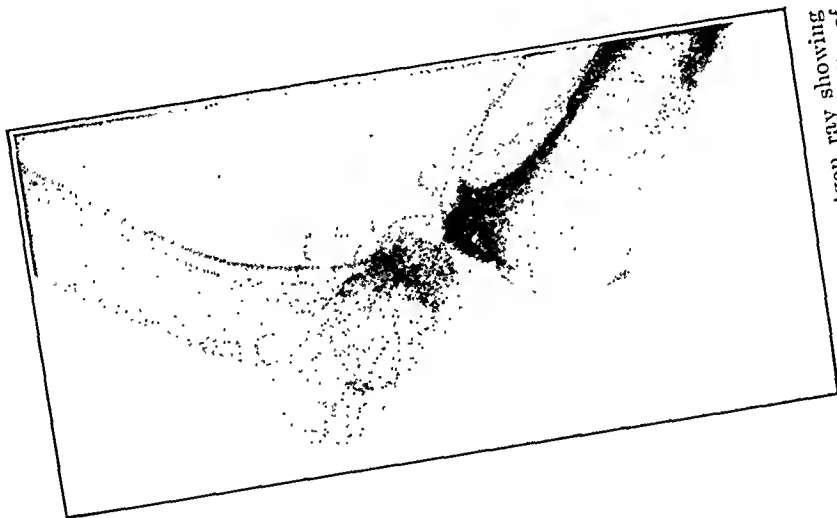


FIG. 5.—Roentgen ray showing the overgrowth of the patella of dog "Wooley" three months after ligation of the patellar vessels.

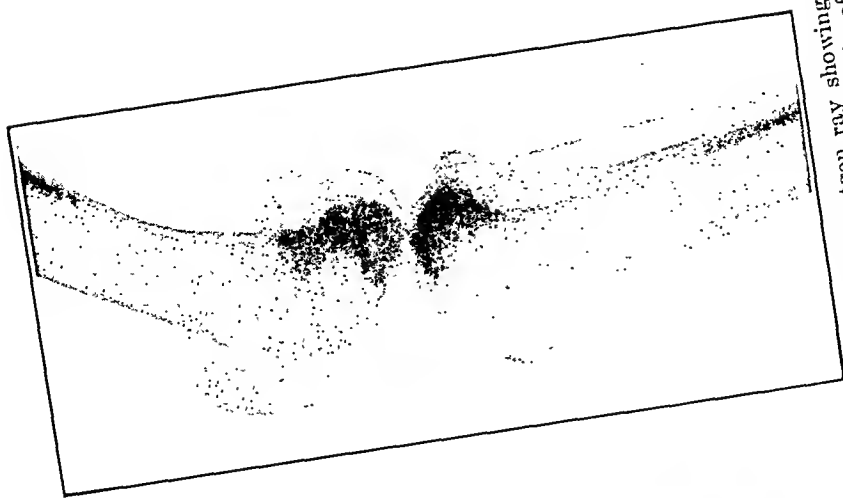


FIG. 6.—Roentgen ray showing the overgrowth of the patella of dog "Wooley" nine months after ligation of the patellar vessels.



FIG. 7.—Roentgen ray showing the normal patella of dog "Yellow." The Roentgen ray was taken before the ligation of the patellar vessels.

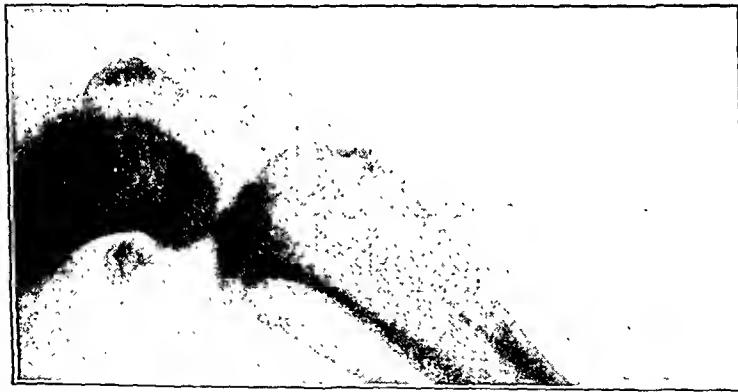


FIG. 8.—Roentgen ray showing the overgrowth of the patella of dog "Yellow" two months after ligation of the patellar vessels.

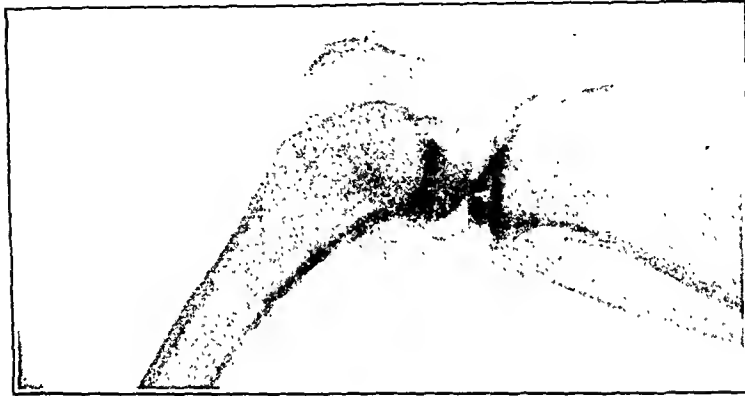


FIG. 9.—Roentgen ray showing the overgrowth of the patella of dog "Yellow" five months after ligation of the patellar vessels.

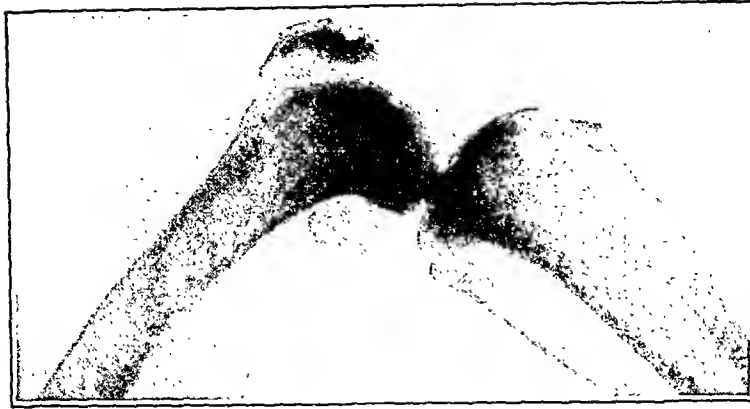


FIG. 10.—Roentgen ray showing the overgrowth of the patella of dog "Yellow" nine and a half months after ligation of the patellar vessels.

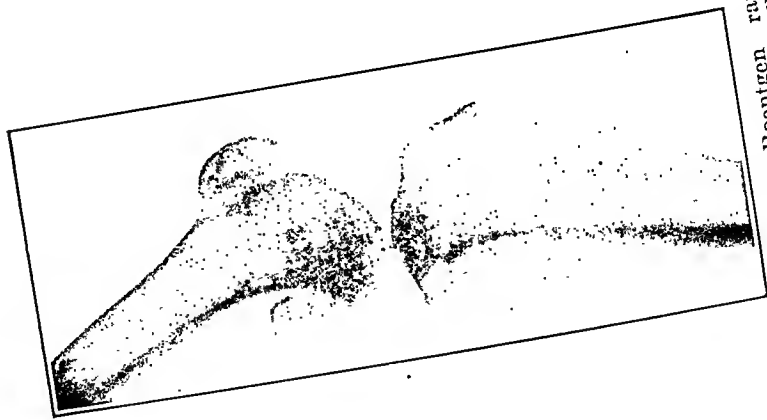


FIG. 11.—Roentgen ray showing the normal patella of dog "Yellow." (The shadow behind the patella is the condyle.)



FIG. 12.—Roentgen ray showing the patella of dog "Yellow" five months after the control operation. The Roentgen ray shows no noteworthy change from the normal.

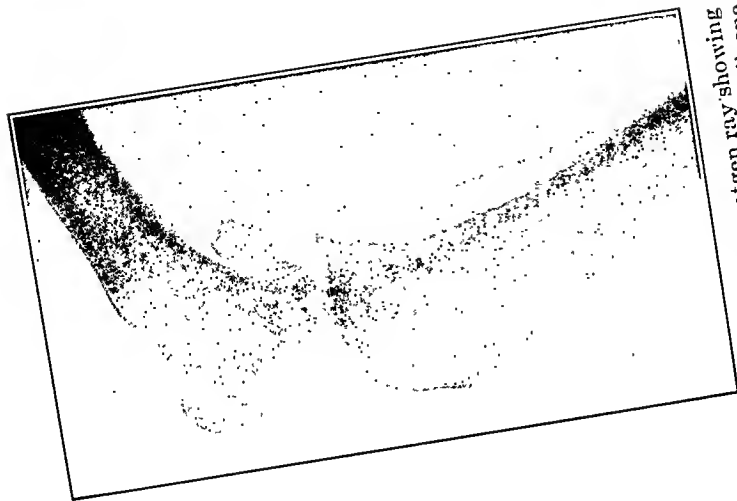


FIG. 13.—Roentgen ray showing the patella of dog "Yellow" one year and three months after the control operation. The Roentgen ray shows no noteworthy change from the normal.

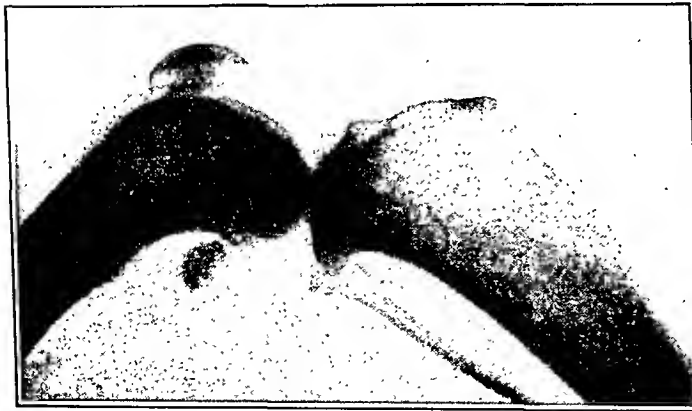


FIG. 14.—Roentgen ray showing the normal patella of dog "Brown." (The shadow behind the patella is the condyle.)

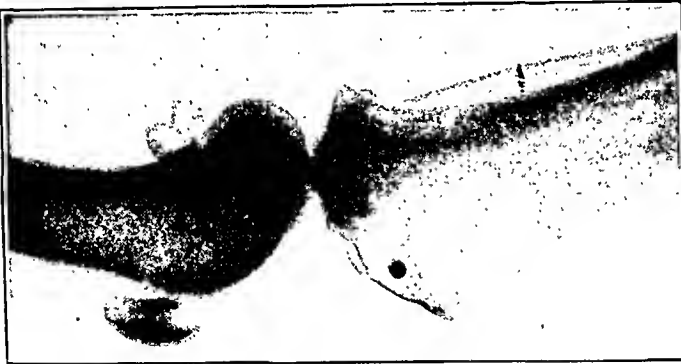


FIG. 15.—Roentgenray showing the patella of dog "Brown" three months after the control operation. The Roentgen ray shows no change from the normal.

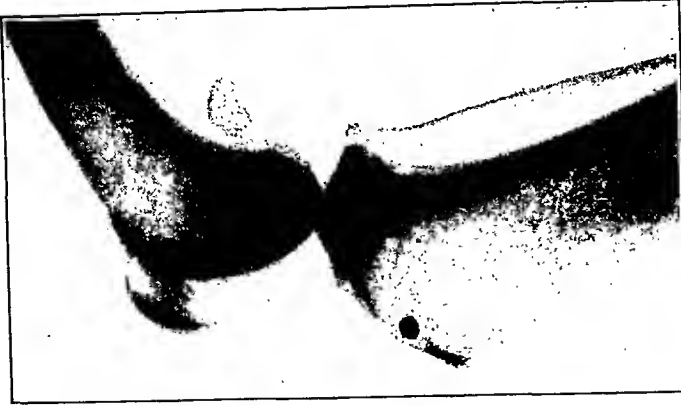


FIG. 16.—Roentgen ray of the patella of dog "Brown" seven and a half months after the control operation. The Roentgen ray shows no change from the normal.



FIG. 17.—Photograph showing the overgrowth of the patella of dog "Irish" nine and a half months after ligation of the patellar vessels. The lower portion of the left patella shows the overgrowth.

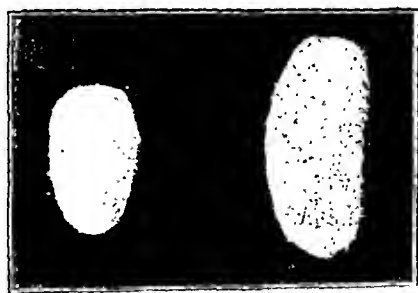


FIG. 18.—Photograph showing the overgrowth of the patella of dog "Wooley" nine months after ligation of the patellar vessels. The lower portion of the right patella shows the overgrowth.

tive in the production of both atrophic and hypertrophic arthritis, the experiments here discussed throw light upon the intermediary mechanism by which the phenomena of the rheumatoid syndrome are brought about, both in the soft and in the bony tissue.

Conclusions. Experiments are reported in which the phenomena of arthritis, chiefly of the hypertrophic variety, are brought about in the region of the patella of dogs by ligation of the blood supply to the patella. Control experiments in which an amount of silk ligature equal to that used in the original experiments was placed around the patella, following upon an otherwise essentially identical operation, failed to produce any overgrowth after a comparable lapse of time.

Analyses of the overgrowth and of the original patella giving rise to the overgrowth show that the percentage magnesium content in these tissues is higher than on the control side. The involvement of the mineral metabolism in the region affected is thus clearly indicated.

These experiments are in entire consonance with those arrived at, following a different line of reasoning, by Wollenberg and indicate beyond any reasonable doubt that disturbance of the blood supply must henceforth be regarded as one of the factors capable of producing arthritic change. Taken in conjunction with other work referred to early in the present text, these experiments afford strong evidence that interference with the blood supply, probably in the nature of vasoconstriction, constitutes at least a part, probably a large part, of the underlying physiologic disturbance productive of the phenomena of chronic arthritis, especially the hypertrophic type as encountered in human beings.

REFERENCES.

1. Pemberton, R., Hendrix, B. M., and Crouter, C. Y.: Studies in Arthritis; the Blood Gases and the Blood Flow, *J. Metab. Res.*, 1922, **2**, 301.
2. Peirce, E. G., and Pemberton, R.: The Red Cell Count in Arthritis, *Arch. Int. Med.*, 1927, **39**, 421.
3. Cajori, F. A., and Crouter, C. Y.: The Red Cell Count in Arthritis, *Arch. Int. Med.*, 1927, **39**, 429.
4. Wright, L. M., and Pemberton, R.: The Peripheral Surface Temperature in Arthritis, *Arch. Int. Med.* 1930, **45**, 147.
5. Pemberton, R., Cajori, F. A., and Crouter, C. Y.: The Effect of Changes in the Circulation on Carbohydrate Utilization, *J. Biol. Chem.*, 1925, **66**, 89.
6. Pemberton, R.: Arthritis and Rheumatoid Conditions; Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929, p. 115.
7. Wollenberg: *Arch. f. Orth. u. Mechano. Unfall. Chir.*, 1909, **7**, 226.
8. Axhausen, G.: *Ztschr. f. Orth. Chir.*, 1913, **33**, 223.
9. Nichols, E. H., and Richardson, F. L.: *J. Med. Res.*, 1909, **21**, 149.
10. Gray, H.: *Anatomy, Descriptive and Applied*, 23d ed., London, Longmans, Green & Co., Ltd., 1926, p. 713.
11. Kramer, B., and Howland, J.: *J. Biol. Chem.*, 1926, **68**, 711.
12. Briggs, A. P.: *J. Biol. Chem.*, 1922, **53**, 13.
13. McCrudden, F. H.: *J. Biol. Chem.*, 1910, **7**, 199.
14. Gassman, T.: *Ztschr. f. Physiol. Chem.*, 1910, **70**, 161.
15. Toverud, G.: *J. Biol. Chem.*, 1923, **58**, 583.
16. Leriche and Policard, translated by Moore and Key: *The Normal and Pathological Physiology of Bone*, St. Louis, C. V. Mosby Company, 1928, p. 66.

SUBPHRENIC ABSCESS.*

BY GATEWOOD, M.D.,

ASSOCIATE CLINICAL PROFESSOR OF SURGERY, RUSH MEDICAL COLLEGE OF THE
UNIVERSITY OF CHICAGO, CHICAGO, ILL.(From the Presbyterian Hospital of Chicago and the Surgical Department of Rush
Medical College of the University of Chicago.)

ALTHOUGH subphrenic abscess was described by Barlow¹ in 1845, it was not until 1879 that the first operation for this condition was done by von Volkmann.² During the past few years, this subject has been studied extensively and as a result much earlier recognition has been possible. Despite this and the development of better operative technique, the mortality has not been correspondingly lowered. According to Moynihan,³ we should expect about 16 per cent mortality. Lockwood's⁴ statistics from The Mayo Clinic gave a mortality of 33.3 per cent in 81 operated cases, with a mortality of 97 per cent in 32 unoperated cases, and Barnard's⁵ original group of 76 cases collected from London hospitals has a death rate of 47 per cent. In a group of 41 cases occurring in the Presbyterian Hospital during the past ten years, the mortality rate is 34 per cent if 3 cases in which no operation was performed are included, or 29 per cent in the operated cases. Sachs⁶ states that in the first three weeks 15 per cent die, but that after this time, the mortality is 50 per cent. His mortality in the unoperated cases was 71.5 per cent and Elsberg's⁷ was 82 per cent.

Etiology. All subphrenic abscesses must be either *primary* or *secondary*. True primary abscesses must be very few and these are probably limited to traumatic infections such as stab wounds, although Lee⁸ has called attention to cases of "spontaneous origin" and a number of idiopathic cases have been reported.

The *secondary* subphrenic abscesses form the great group most frequently encountered by the surgeon. They are the result of (1) direct extension from a neighboring primary focus, or of (2) lymphogenous infection from a more remote source, or of (3) blood-stream infection. Naturally, most subphrenic abscesses are the result of *direct spread* of the infection, from such sources as a perforation of the stomach, appendix or gall bladder, or they form as a walled-off abscess in general peritonitis.

The relative frequency of these primary sources as the causative factor varies with the type of patient seen in the individual clinic, although in most series perforation of the stomach heads the list, and appendicitis follows closely. Even today with the earlier diag-

* Read at the meeting of the Western Surgical Association, December 13, 1929, Del Monte, Calif.

It is frequently difficult to exclude other methods of infection, but there is no doubt that the *lymphatics* can carry infection to the subphrenic space in the same way that carcinomatous involvement occurs on the under surface of the diaphragm. The lymphatic connections between the subphrenic spaces and the abdominal viscera, according to Dexter,¹⁰ are threefold: (1) The retroperitoneal cellular tissue; (2) from around the epigastric artery to the falciform ligament, which is in close association with the lymphatics of the appendix and colon, and (3) the subphrenic lymph spaces which pass through the diaphragm, connecting with the pleural plexus of lymphatics. Although infection usually travels from below upward, it may proceed from the pleural cavity downward. In 190 cases of empyema observed by Beye,¹¹ secondary abdominal infection was encountered in only one case. On the other hand, there were 9 cases of empyema secondary to subphrenic abscess.

The primary foci of the subphrenic abscesses observed at the Presbyterian Hospital in the past ten years have been classified as follows:

- * It has been impossible to determine the exact route the infection has taken in these cases.

* It has been impossible to determine the exact route the infection has taken in these cases.

CHART.

Case.	Sex.	Age.	Location.	Etiology.	Complications.	Duration before operation.	Outcome.
1. 88812	Male	15	Right	Suppurative appendicitis (abdominal drainage)	21 months	Cured
2. 93418	Male	39	Right	Ruptured appendix	Right-sided empyema	3 weeks (after operation, 6 years)	Cured
3. 94092*	Female	30	Right	Appendiceal abscess	Indeterminate	Cured
4. 98101	Female	38	Right	Echinococcus cyst of liver	12 days	Cured
5. 105507	Male	49	Multiple	Perforated duodenal ulcer	Severe diabetes	4 weeks	Died
6. 108975	Male	41	Right	Suppurative appendicitis (ruptured)	(no operation)	Cured
7. 121981	Female	45	Right	Perforated gastric ulcer	Pelvic abscess	3 weeks	Cured
8. 133863	Male	29	Right	Appendicitis	Empyema	27 days	Died
9. 135068	Male	11	Extraperitoneal (central)	Appendicitis	3 months	Cured
10. 143116	Male	32	Right	Carbuncle on neck	10 days	Cured
11. 150252	Female	29	Right	Acute appendicitis	Empyema	2½ months	Improved
12. 153395	Male	57	Right	Actinomycosis	Unknown	Improved
13. 158696	Male	44	Right	Hydronephrosis, renal calculus	Postoperative sepsis	4 weeks	Cured
14. 176200	Male	46	Left	Perforated duodenal ulcer	Suppurative pylethrombophlebitis, localized pelvic abscess	2 months (no operation)	Died
15. 177257†	Female	45	Right	Cholelithiasis and biliary fistula	11 months	Died
16. 177477	Female	36	Right	Ruptured appendix	Postoperative bronchial pneumonia	5 days	Died
17. 179076†	Female	38	Left	Perforation of esophagus	Carcinoma of cardiac orifice	24 days	Improved
18. 184225§	Male	35	Right	Cholelithiasis, cholecystitis, ruptured gall bladder	Unknown	Cured
19. 190404	Female	51	Right	Hysterectomy	3 weeks	Cured
20. 190989	Male	35	Left	Stab wound followed by left-sided pelvic abscess	Empyema and pulmonary embolism	10 weeks	Died

21.	191437	18	Left	Renal tuberculosis, perirenal abscess	26 days	Cured
22.	194545	42	Right	Perforated duodenal ulcer	Pleurisy with effusion	6 months	Cured
23.	196523	42	Right	Probably gall-bladder disease	Pyopneumothorax	Unknown	Died
24.	197495	50	Left	Diverticulitis, hernia of diaphragm	Cured
25.	199720	8	Left	Empyema	Perforation of diaphragm	20 days	Cured
26.	202987	24	Right	Appendicitis	Lung abscess	4½ months	Improved
27.	204824	27	Right	Chronic cholecystitis	Multiple abscesses of liver, diabetes	3 weeks	Died
28.	205438	33	Right	Perforated duodenal ulcer	Duodenal fistula	36 hours	Died 17 days after operation
29.	205757**	52	Right	Perforated gastric ulcer	6 months	Died
30.	208267	51	Right	Perforated ulcer	Retroperitoneal infection	6 weeks	Died
31.	212982	46	Left	Carcinoma of stomach with perforation	Peritonitis	Unknown, short	Died at end of 10 days
32.	214407	52	Right	Herniotomy	Paralytic ileus	4 weeks	Improved
33.	219916	60	Right	Cholecystitis (postoperative)	8 days	Cured
34.	222128	31	Right	Perforated ulcer	14 hours	Cured
35.	223138	48	Right	Perforated ulcer	About 10 days	Cured
36.	228863	40	Left	Perforated ulcer	Right-sided empyema	About 4 weeks	Died
37.	229962††	23	Right	Pyelitis of pregnancy	Pleural effusion	20 days	Cured
38.	230871	42	Right	Perforated ulcer	Liver abscess	15 days	Cured
39.	233492	35	Right	Perforated duodenal ulcer	Right-sided empyema	14 days	Died
40.	236974	56	Right	Cholelithiasis, cholecystitis	16 days	Cured
41.	X54438	30	Left	Pancreatitis	Cholecystitis	3 weeks	Cured

NOTE.—Cures are indicated where the ultimate result is known. Those marked improved have not been followed since they left the hospital, or are not well.

* Appendiceal abscess drained four years previously. Appendiceal fistula preceding abscess. Acute.

† Subphrenic secondary to operation to close fistula.

‡ Recovered from subphrenic. Died 14 months later.

§ Transpleural drainage.

|| Fluoroscopy shows no movement of the diaphragm on the left side.

** Empyema developed 5 weeks after operation followed by lung abscess and bronchial fistula.

†† Transpleural drainage in the anterior axillary line.

The *pathology* is that of an abscess in areolar tissues or of localized peritonitis. The abscesses are either *acute* or *chronic*. The latter may not be recognized for weeks, months or even a year or more, and cause the greatest difficulty in diagnosis. In one of our cases, four years lapsed between the primary and the secondary operation. Perforation into a viscus is rare, but may occur into the stomach, the colon, the pleural cavity, the pericardium, or even into a bronchus. Spontaneous rupture through the abdominal wall formerly was not uncommon, but is now quite rare. Various organisms have been found, the colon bacillus being present in the great majority of cases. The gas found in one-third (Loekwood) to one-fourth (Ullman and Levy¹²) of cases is usually the result of bacterial action.

Much discussion of the subphrenic spaces has led to various subdivisions, largely on anatomic grounds. Nather¹³ has divided the suphrenic space into supra- and subhepatic divisions limiting the inferior border to the transverse colon and mesocolon. The spaces above the liver may be divided into right and left by the falciform ligament and these in turn into the large anterior and small posterior by the coronary ligaments. In addition to these intraperitoneal spaces, extraperitoneal infections occurring between the reflected peritoneal borders of the coronary and falciform ligaments have been described by Braun. In our present series we have not included subhepatic abscesses as suggested by Nather and it has been impossible to classify the cases except as right sided or left sided with one extraperitoneal abscess. There are 30 on the right side, 9 on the left, one multiple and one extraperitoneal (central).

Diagnosis in the early cases ordinarily is not difficult, although 2 of our patients came to autopsy without the condition being recognized and a third, though suspected, was not operated upon. As Tuft,¹⁴ says, "suspect subphrenic in all postoperative patients who are not doing well." The history is all important, especially in the older cases, where the diagnosis may be exceedingly difficult. Although the onset usually is insidious, Fagge¹⁵ calls attention to the fact that in some cases the symptoms begin abruptly. The patient looks and feels sick. Fever, chills and sweats are significant. The temperature is usually of the church-steeple character, suggesting pus under tension. The respiratory rate may not be in keeping with the temperature. Hiccough is always a suspicious sign although it occurs in only about a half of the cases. A cough as the result of diaphragmatic irritation has been mentioned by a number of authors but has been present in but few of our cases. Shortness of breath and difficulty in breathing vary with the amount of compression of the lung and with the amount of secondary pulmonary involvement. Epigastric pain may be marked or very slight, but subcostal tenderness is usually present. Pain in the root of the neck is frequently present.

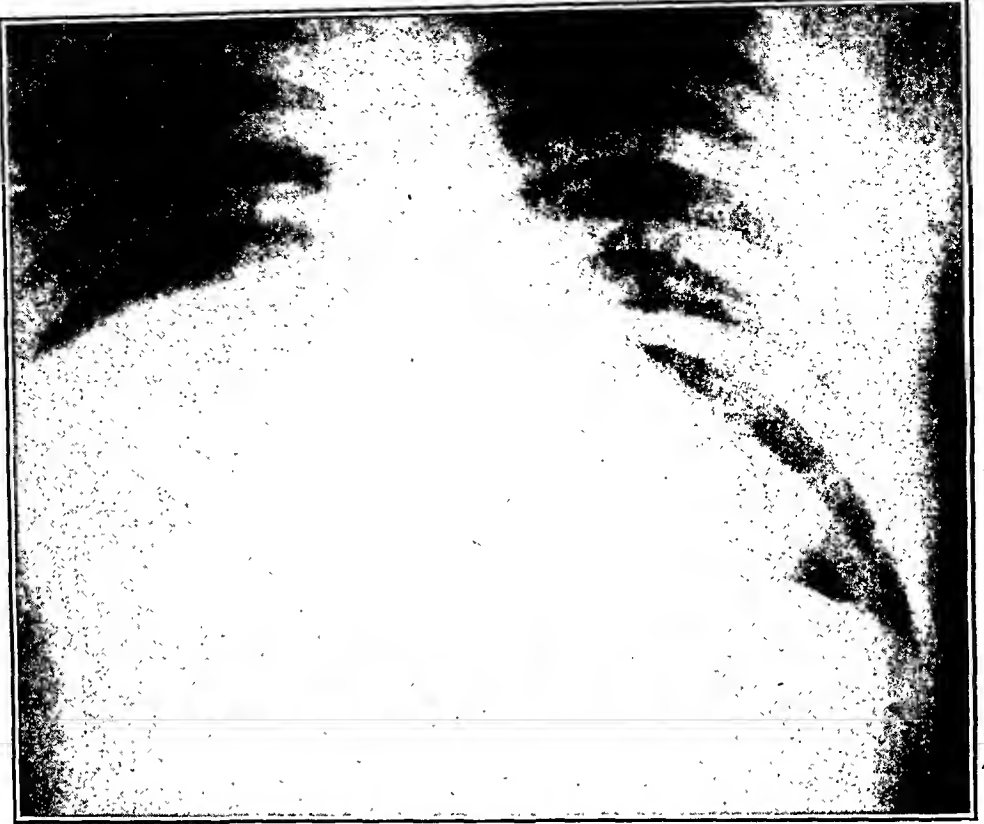


FIG. 1.—Case No. 222128. Subphrenic abscess showing elevation of right diaphragm with fluid level and gas bubble above it.

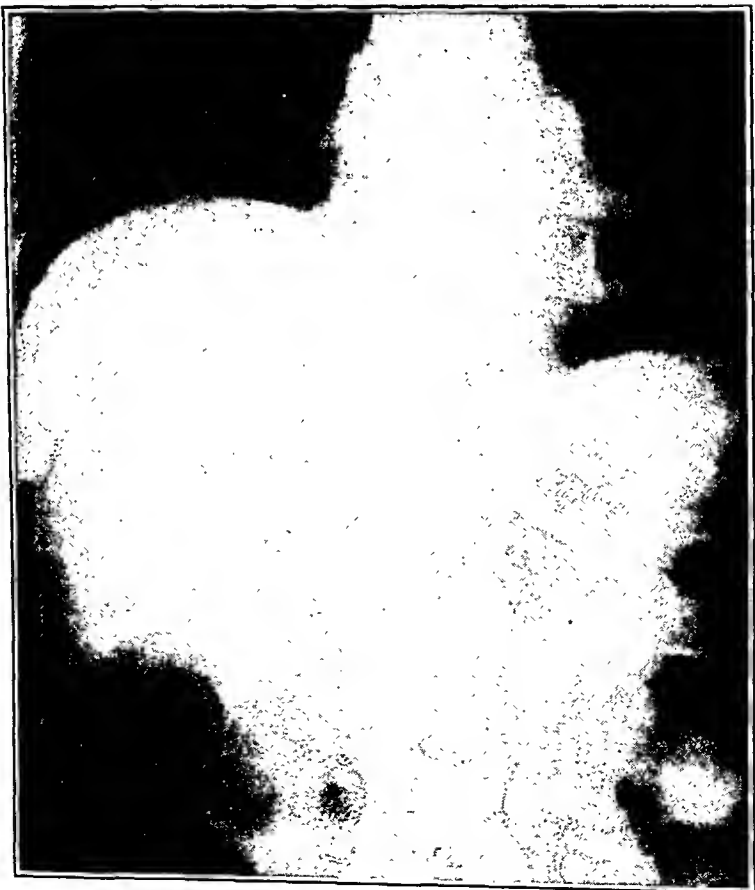


FIG. 2.—Case No. 223138. Subphrenic abscess demonstrated by lipiodol injection.

Subphrenic abscess must be differentiated from empyema, liver abscesses and neoplasms, and perinephritic abscess. This can usually be done by obtaining a good history, especially with reference to a possible primary focus, by accurate physical findings and careful Roentgen ray examination.

Physical examination reveals a sick individual with flatness as a rule on the infected side due to the elevation of the diaphragm. Older observers stress the presence of breath sounds through this flattened area but compression of the lung and the presence of fluid in the pleural cavity make this sign difficult to elicit and rather unreliable. Air in the abscess cavity may give a tympanitic note instead of the flatness and on the left side gastric tympany may complicate the picture. Tuft calls attention to the fact that the heart may be displaced upward but not laterally. Bulging in the epigastrium or on the infected side in the region of the lower ribs occurs in most late cases. Edema and redness of the overlying skin is frequently observed. The liver is usually displaced downward. The leukocyte count varies from 16,000 to 40,000, being highest in those cases complicated by liver abscess. The Roentgen ray gives us the most important information upon which to base our diagnosis. Fluoroscopically, the diaphragm on the infected side is smoothly elevated as contrasted with the irregularities due to old pleural adhesions or to the nodular irregularities of metastatic liver carcinoma and liver abscess. The splinting of the diaphragm is very noticeable and much more marked than in diaphragmatic paralysis or in lesions of the liver. Pancoast¹⁶ believes that careful Roentgen ray examination should enable one to differentiate a subphrenic abscess from liver abscess, gumma, or from intrahepatic tumors. Paolini and D'Istria¹⁷ report a case diagnosed by pneumoperitoneum and agree with Sante¹⁸ upon its value as an aid. I should hesitate to use this method and Pancoast does not think it is of great value. Careful study of the films taken in the upright position often aids in the Roentgen ray diagnosis. The presence of a fluid level below the diaphragm should always be sought for but cannot be found in more than a half of the cases (Fig. 1). The cavity has been demonstrated in 3 of our cases by the injection of opaque contrast material such as lipiodol¹⁹ (Fig. 2).

The *treatment* is essentially surgical as soon as a definite diagnosis is made. The method of approach must vary with the location of the abscess and the concomitant pathology. Statistics are of little value in determining the best method of approach and one should be governed by the findings in the individual case.

When the abscess points in the epigastrium, or in the subcostal space, drainage is best accomplished by the abdominal route. Sufficient walling off has taken place to prevent further spread provided care is exercised in exploration. The thoracic approach, either by the subpleural or transpleural method is advocated by

Lockwood and many others. It provides for a direct approach in the high-lying abscesses. Resection of the eighth or ninth rib on the right side (the seventh or eighth on the left) in the posterior axillary line, and careful suture of the pleural layers together before opening the abscess should prevent empyema, but does not in many cases. In this series of 38 cases operated upon, 27 were opened abdominally and 7 transpleurally. In 2 the subpleural method was used and in 2 a combined operation was employed. In 3 of the transpleural cases, empyema did not follow. Ochsner and Nather²⁰ have described a subpleural method which consists in resecting the twelfth rib and draining posteriorly above the kidney. They maintain that it permits drainage of infra- as well as suprahepatic abscesses, and that it is safer than either of the previously mentioned methods. (I have tried the method but once and failed to find the abscess which I subsequently drained abdominally.) The use of the aspirating needle has been condemned, but I have seen no harm result from the use of a moderate-sized needle, provided one is prepared to carry out what further operative technique is indicated.

Summary. 1. A review of the literature and of 41 cases observed in the Presbyterian Hospital during the past ten years, shows that the mortality in subphrenic abscess is still much too high—30 per cent or more.

2. In spite of improved diagnosis methods and earlier operation, acute appendicitis ranks high as an etiologic factor—second in our series.

3. The importance of prophylactic treatment cannot be over-emphasized. Early diagnosis of appendiceal and other contributory causes and their prompt elimination will prevent the formation of many subphrenic abscesses. Adequate drainage and the adoption of the semisitting posture in all lower abdominal infections are two most important preventative measures which should not be forgotten.

4. Finally, attention is again called to the failure to consider the likelihood of subphrenic abscess in any patient not doing well after an abdominal operation, even though performed months previously.

NOTE.—I want to express my thanks to the various members of the hospital staff who have permitted me to include their cases in the compilation.

BIBLIOGRAPHY.

1. Barlow, G. H.: *London Med. Gaz.*, 1845, 1, 13.
2. von Volkman, R.: Quoted from *Keen's Surgery*, 1906, 1, 268.
3. Moynihan, B.: *Abdominal Operations*, 3d ed., 1914, 1, 149.
4. Lockwood, A. L.: *Surg., Gynec. and Obst.*, 1921, 33, 502.
5. Barnard, H. L.: *British Med. J.*, 1908, i, 371.
6. Sachs, W.: *Arch. f. klin. Chir.*, 1895, 1, 16.
7. Elsberg, C. A.: *Ann. Surg.*, 1901, 34, 729.
8. Lee, R. I.: *J. Am. Med. Assn.*, 1915, 64, 1307.
9. Russell, T. H.: *Ann. Surg.*, 1929, 90, 238.
10. Dexter, R.: *Am. J. Med. Sci.*, 1925, 170, 810.

11. Beyc, H. L.: Arch. Surg., 1927, 14, 240.
12. Ullman, A., and Levy, C. S.: Surg., Gynec. and Obst., 1920, 31, 594.
13. Nather, K.: Arch. f. klin. Chir., 1922, 122, 24, abstr. J. Am. Med. Assn., 1923, 80, 362.
14. Tuft, L.: AM. J. MED. SCI., 1925, 170, 431.
15. Fagge, C. H.: Lancet, 1921, i, 571.
16. Pancoast, H. K.: Am. J. Roentgenol., 1926, 16, 303.
17. Paolini, R., and D'Istria, A.: La Riforma med., 1928, 44, 909.
18. Sante, L. R.: J. Am. Med. Assn., 1923, 80, 464.
19. Mullen, B. P.: Surg. Clin. North America, 1929, 9, 467.
20. Ochsner, E. W. A., and Nather, K.: Surg., Gynec. and Obst., 1923, 37, 665.

REMOTE SYMPTOMS OF UNRECOGNIZED THYROID ADENOMATA.

WITH LOW BASAL METABOLIC RATE RELIEVED BY OPERATION.

By P. K. GILMAN, M.D.,

CLINICAL PROFESSOR OF SURGERY, STANFORD UNIVERSITY MEDICAL SCHOOL,

AND

W. E. KAY, M.D.,

CLINICAL INSTRUCTOR OF MEDICINE; CHIEF OF ENDOCRINOLOGY, STANFORD UNIVERSITY
MEDICAL SCHOOL, SAN FRANCISCO, CALIF.

DURING the past four years a number of private patients have presented themselves complaining of symptoms that had previously led to various diagnoses by competent physicians. Our interest in diseases of the thyroid gland led us to what we think is the correct explanation of these symptoms. In some of these cases, in spite of this special interest, the diagnosis remained obscure for some time and was then stumbled upon more or less accidentally. With the above in mind we made a careful search of the clinic records of the past ten years at Stanford University Medical School and were unable to find any case for inclusion in this report. Apparently such cases were not recognized.

In the patients reported in this paper the classical signs of thyroid toxicity were for the most part absent. Furthermore the basal metabolic rate in each instance was either normal or below normal. In many instances the patients were more or less indefinite in their complaints but were unanimous in stating that they did not feel well and knew something was definitely wrong.

Thirteen cases coming to us during the past four years furnished material for this report. Their symptoms largely directed attention away from the thyroid gland and suggested trouble with systems elsewhere in the body.

Nervousness was the most frequent symptom. This nervousness was not suggestive of the type usually met with in thyrotoxicosis.

It was in the nature of a nervous tension and sense of apprehension, associated with a feeling of carrying too heavy a load. As a rule this symptom was brought out only after careful questioning, thus differing from the objective nervousness usual in hyperthyroidism. To further illustrate this type of nervousness it may be added that several of these patients had been classified as psychoneurotics, chiefly of the neurasthenic type.

Weakness, fatigability and palpitation were common symptoms and present in nearly all of the cases. These with shortness of breath had evidently led to a previous diagnosis of cardiovascular disease in nearly a half of these patients.

Five of the 13 patients exhibited a definite hypertension, 3 showing a high diastolic pressure and cardiovascular damage. The other 2 showed definite heart and bloodvessel changes but to a lesser degree.

Attention was directed especially to the gastrointestinal tract in 3 of the patients. In one, the patient had been previously treated for over a year for gall-bladder disease and colitis; a second, diagnosed as sprue, had been treated for a chronic enteritis, for five years. The third had been under treatment for stomach trouble.

One patient had had a chronic cough and had been diagnosed as having pulmonary tuberculosis.

Among the less frequent symptoms, loss of weight was present twice; dizziness was complained of twice; tremor of the fingers but once. A feeling of warmth was not complained of in any instance in this series.

The pulse rate was usually a little increased but seldom over 80 per minute. In 2 cases the rate was between 60 and 70 per minute.

The following abstracts of case histories of a few of the patients illustrate the points we have endeavored to emphasize in this communication:

Case Abstracts. CASE I.—Mrs. A. W., aged seventy-two years, widow, complained of stomach trouble consisting of discomfort two hours after eating, gas and frequent cramps in the lower abdomen. In addition fatigability and weakness were symptoms. All of these had been present for two years. Lately the symptoms had become worse. The patient had been told she was suffering from a diseased gall bladder and colitis.

Examination showed a fairly well preserved and nourished elderly woman. Her eyes were rather bright but otherwise negative. There was a very slight enlargement of the thyroid, which was firm and apparently finely nodular. No bruit was heard. The heart was slightly enlarged and of the aortic type. The apical tones were rather loud with a soft systolic murmur and the second aortic moderately accentuated. The heart's efficiency was judged to be about 80 per cent. The aorta was moderately widened and of the arteriosclerotic type. The radial vessel walls were moderately thickened; the pulse 80 per minute and the blood pressure 150 over 70. The abdomen showed some tenderness to deep pressure in the gall-bladder region and over the sigmoid colon. There was a moderate-sized fibroid of the uterus. The reflexes were normal.

Although this patient when first examined appeared to be composed, on further observation she was found to be nervous. Her palms were always slightly warm and moist but the extended fingers showed no tremor. She gave a history of having been quite active until two years ago since when she had tired much more readily.

Our first impression caused us to accept the previous diagnosis of gall-bladder disease and colitis. Ulcer of the duodenum was also considered. In addition we made a diagnosis of arteriosclerosis of moderate grade with aortitis and myocarditis. Further a mild grade of hyperthyroidism was suspected and a basal metabolism taken which was normal. A Roentgen ray study of the gastrointestinal tract showed no organic lesion.

This patient was kept under observation for about a year and a half, during which time she showed periods of improvement. During this entire time her complaints were referable for the most part to her gastrointestinal tract. The cramps in the lower abdomen were complained of more than ever and were frequently accompanied by diarrhea. It was noted she became more nervous and tired more readily. Her pulse rate remained about the same and her basal metabolic rate rose as high as +13. During the course of treatment Lugol's solution was given, following which, for a time, her symptoms were much less but later were increased.

Finally the observable increase in nervousness, palpitation of the heart, slightly moist warm palms and the effect of iodine in addition to the complete failure of other treatment led us to suspect the small, finely nodular thyroid gland as the cause of the patient's symptoms. We hesitated to operate because of her age and lack of definiteness of demonstrable thyroid participation. Consultants blamed the cardiovascular system and colitis for the patient's condition but later felt it would be worth while to eliminate a possible thyroid element by operation as the patient was getting nowhere.

At operation the thyroid gland was found to be larger than had been previously suspected and was riddled throughout with small adenomata. The largest of these was not over 3 mm. in size. The greater part of the gland was removed.

After an uneventful convalescence all of the patient's symptoms disappeared and she has been well now for two and a half years.

CASE II.—Mrs. B. P., aged thirty-six years, married, had been under the care of a doctor for some time for neurasthenia and a nervous breakdown. She complained of nervousness and tiring easily and at times of palpitation of the heart. There was no loss of weight nor any special digestive disturbance. She felt the cold keenly and complained of her hands being cold and moist. This latter she had observed especially as she was an operator in a beauty parlor.

Examination showed the patient to be nervous. She was well nourished, the skin was a little dry and the supraclavicular fat pads were noticeable. The eyes beyond being somewhat bright were negative. The neck showed a moderate diffuse enlargement of the thyroid gland, suggesting a colloid goiter. This slight enlargement had been present for fifteen years according to the patient.

The heart tones were somewhat loud at the apex and there was a soft systolic murmur not transmitted. The second aortic was of moderate intensity. The blood pressure was 140 over 70, the pulse 80 per minute when standing and 66 per minute when the patient was lying at rest. The lungs showed harsh bronchovesicular breath sounds at the left apex with a few crackles after coughing. The patient's reflexes were hyperactive, the palms slightly cool and moist. There was no tremor. The basal metabolic rate was -9. Further study of her chest showed no definite lesion and she was placed on thyroid extract 0.016 gm. once daily and a mixture containing phenobarbital and sodium iodid.

For about a month the patient stated she felt improved and the thyroid gland seemed smaller although no actual measurements were taken. The pulse rate ranged between 72 and 76 per minute standing and with the patient at rest was the same as before—66 per minute. The basal metabolism showed a rate of +1.

Following this period of improvement the patient became worse again and this encouraged us sufficiently to advise operation. The picture however was not a definite one and we operated with some trepidation. A condition of adenomatosis was found and a subtotal thyroidectomy done.

The recovery from the operation was uneventful. To our gratification and somewhat to our surprise all symptoms disappeared promptly. A year later the patient stated she had never felt better in her life. Her basal metabolism, three months after operation, was +1.

CASE III.—Mrs. C. G., married, aged forty-nine years, was sent to us with the following diagnosis: Severe hypertension, myocarditis, arteriosclerosis and nephritis. She complained of bad headaches, shortness of breath, fullness in the head and neck and fatigability. Further questioning brought out that the patient was quite nervous, complained of hot flashes and that she dated her symptoms back two years.

Our first examination supported the previously made diagnoses. She was placed on treatment including sedatives in the form of phenobarbital, ovarian injections for dysovarianism and bloodvessel spasm, heparmone for the reduction of blood pressure, digitalization and a diet.

The patient improved somewhat, the headaches becoming less pronounced, the shortness of breath somewhat less and the blood pressure lowered from 195 right, 190 left, over 100 to 175 right and left over 100. The treatment was carried out for about four months, the patient during this time being unable to do any housework and confined for the most part to bed. She still complained of marked weakness, nervousness, oppression in the head and shortness of breath.

After close scrutiny it was noticed one day that there was a slight fullness of the neck low down in front. This led to a more thorough investigation which revealed some small nodules identified as being connected with the thyroid gland. These felt about the size of the end of the small finger. Consultation with one of us confirmed this. A basal metabolism was taken and found to be +5. The patient's pulse was about 80 per minute.

Another two months intervened during which period she made little if any progress. We then explained to her the possible effect of these nodules upon her condition and advised their removal although we made it plain that we could not promise anything. On the other hand it was explained to her that no other therapeutic measures suggested themselves.

The patient proved very willing to coöperate and a subtotal thyroidectomy was performed. At operation the right lobe of the thyroid was found to be much larger than had been anticipated, the enlargement being due to the presence of several adenomata the largest of which was less than 2.5 cm. in diameter.

Convalescence was normal and the result of the operation very pleasing. About six weeks later the patient volunteered she had not felt so well for years. Her strength had markedly increased, the shortness of breath and palpitation had disappeared together with the sense of oppression and headaches. She no longer felt nervous. Three months later this patient asked us if it would be safe for her to go from house to house as a saleswoman in addition to doing her housework. At this time her blood pressure read 150 over 90. Her heart tones were of better quality, her pulse 72 per minute and the previous faint trace of albumin in the urine had disappeared.

CASE IV.—Mrs. C. J. B., married, aged twenty-eight years had been ill for four years. Tuberculosis, heart trouble and chronic sinus disease had been suspected. She had had her tonsils removed and was to have undergone a nasal operation. She complained when coming to us of weakness, fatigability, loss of weight, cough, shortness of breath, palpitation and menstrual irregularities.

Examination showed a thin, sick-looking young woman with rather high color in her cheeks. Her eyes were somewhat bright and slightly prominent, the latter being a familial characteristic. The nose showed some intranasal catarrh. The thyroid gland was slightly enlarged and smooth but firm especially on the right side.

The lungs showed harsh bronchovesicular sounds in the right upper lobe with fine râles on occasions which seemed superficial and were probably muscular. The heart was moderately enlarged, the tones loud and thumping with no murmurs. The bloodvessel walls were slightly thickened, the pressure 130 over 90, the pulse 90 per minute. There was no tremor of the fingers, the palms were cool and moist. The patient's reflexes were hyperactive. Our impressions from the examination included chronic intranasal disease, slight goiter with questionable thyrotoxicosis, questionable pulmonary tuberculosis and secondary anemia. A Roentgen ray of the chest showed nothing beyond some hilus thickening. Patient's basal metabolic rate was -13 .

Treatment consisted of iron cacodylate injections, high-caloric diet and syrup of hydriodic acid, which resulted in considerable improvement. Later small amounts of thyroid extract were given as we believed the goiter was a colloid condition with hypothyroidism. The patient during this period of treatment, about two months, was being prepared for a nasal operation. She however failed to return and was not seen again for two years. At this time her complaints were largely the same as before with an added symptom of heart flutter with sudden stoppage, the history of which was characteristic of paroxysmal tachycardia. Reëxamination revealed practically the same findings as the first, the basal metabolic rate was -14 . She responded unfavorably to thyroövarian extract in small amounts. On the occasion of a subsequent visit sometime after discontinuing thyroid medication this patient more forcibly impressed us as a person under a nervous strain. On examining the thyroid again we felt it was possibly the seat of an adenoma. It was explained to the patient that in spite of her low basal metabolic rate her thyroid might be the cause of her troubles and operation was advised.

At operation a smooth, rounded adenoma measuring 4.5 cm. in diameter was removed from the lower right pole. This adenoma blended with the rest of the lobe rendering its clinical recognition difficult if not impossible. The left lobe of the gland was normal.

An uneventful convalescence preceded a complete return to health and the patient has been well now for nine months.

CASE V.—Miss S. G., single, aged fifty-four years had been treated for heart trouble and tuberculosis for two years. She complained of a queer feeling in her head, cough, palpitation of the heart at times and some shortness of breath. On further questioning, she also complained of fatigability, nervousness and hot flashes.

She first consulted one of us five years ago at which time examination showed a large, well-nourished woman, somewhat nervous, with a face that flushed easily. Examination of the thyroid seemed negative. Her lungs showed wheezing throughout. Her heart was moderately enlarged, of the aortic type, with sounds which were loud and thumping. There was a soft systolic murmur at the apex and a rather loud systolic murmur at the base.

The second aortic was accentuated and ringing. The aorta was moderately widened throughout and of the arteriosclerotic type. The blood pressure was 160 over 100, the pulse 80 per minute. The vessel walls were moderately thickened. A preliminary diagnosis of arteriosclerosis, hypertension chronic, aortitis, myocarditis, bronchitis chronic, and intranasal disease was made. Patient was given a hypertension diet, syrup of hydriodic acid and phenobarbital.

She improved considerably and after a few visits was not seen again for a year when she returned complaining of cough and shortness of breath. She improved on digitalis and was seen by a throat specialist who diagnosed chronic sinusitis and advised a nasal operation. This was not done and the patient again ceased coming for a year and a half. At this time she complained of a return of all of her symptoms. In addition it was observed she was more nervous than before and that her palms were a little moist and warm. There was a slight tremor of the extended digits and she complained more of hot flashes than previously. Patient was sent to the hospital for two weeks and in the course of her examination her basal metabolic rate was determined to be -12 .

She was given ovarian injections, bromide and digitalis. Later small amounts of Lugol's solution were given in spite of the low basal rate and because some of the symptoms, as in other cases, suggested over action of the thyroid. This was followed by a period of rather marked improvement, the heart palpitation disappearing and the pulse slowing to 70 per minute. Six months later the patient returned seemingly worse than ever and one day when talking to her a small lump was observed to rise from behind the left sternoclavicular region when she swallowed. This was the first intimation we had of any gross abnormality in the thyroid and we immediately followed this lead as the probable cause of at least some of her symptoms. Her basal rate was then $+5$.

Operation was agreed upon and a substernal adenoma 4 cm. in diameter attached to the lower left pole as well as several small adenomata of the right lobe were removed.

Two months later the patient stated she had never felt better and that a load had been taken from her head and shoulders. She was no longer nervous, showed very little shortness of breath and her cough had disappeared. Her pulse was 68 per minute, the heart tones were of much better quality and her blood pressure was 130 over 80. The tremor of the fingers and warmth of the hands had disappeared.

A great compensation to us was the feeling of gratitude and encouragement that these patients demonstrated after long periods of discouragement with their seemingly hopeless condition.

Conclusions. 1. Unrecognized thyroid adenomata as a cause of remote symptoms are frequently overlooked.

2. In patients exhibiting combinations of symptoms such as we have attempted to describe, with failure of improvement under medical treatment, adenomata of the thyroid must be carefully excluded as the underlying cause.

3. Toxic adenomata are not necessarily accompanied by an increased basal metabolic rate but may be present with a normal or subnormal rate.

4. The improvement these patients exhibit following operation is most striking and gratifying.

ANOREXIA NERVOSA, ANOREXIA, INANITION, AND LOW BASAL METABOLIC RATE.*

BY JOHN M. BERKMAN, M.D.,

FELLOW IN MEDICINE, THE MAYO FOUNDATION, ROCHESTER, MINN.

ONE hundred and seventeen cases fundamentally alike clinically and diagnosed anorexia nervosa were found in a review of the cases in which examinations had been made at The Mayo Clinic from the beginning of 1917 to the end of 1929.

The term anorexia nervosa was introduced in medical literature by Sir W. W. Gull in 1868. He presented a paper on the subject in 1873, which was published in 1888. Lasègue, in 1874, wrote a paper in which he commented on a similar condition but gave as its cause, early tuberculosis. Until 1900 the literature on anorexia nervosa consisted of reports of cases, of which there were many, comments on the disease, and criticisms. Since 1900 the reports have been contributed by Europeans, mainly the French and the Germans.

Publications on the subject in this country have been limited. Several articles have been published, however, relative to a large group of cases in which the basal metabolic rate was low, and in some cases the causal factors have been attributed to psycho-neurosis and inanition.

Leede, in a publication on anorexia nervosa, considered the condition to be pluriglandular in origin, and he expressed the belief that suprarenal insufficiency plays the most important part. In his opinion, hypoglycemia is present and in his treatment of the condition he included intravenous administration of solution of glucose and injections of epinephrin. In the cases which I have reviewed, hypoglycemia has not been found.

It seems best, at this point, to give a generalized description of the appearance of these patients, their mental reactions, and the clinical history. As to their appearance, two striking characteristics attract the physician's attention at first glance: the extreme emaciation and the rather marked pallor. The pallor has led the physician to include, in recording his observations in the preliminary examination, notations referable to the presence of rather severe anemia. Questioning draws attention to certain prominent features in the mental reaction of these patients. They appear preoccupied, sit with the head bent and gaze at the floor, but when questioned, they quickly respond. However, once the question is answered, they resume the apathetic manner. They are reticent in answering questions directly concerning their mental attitude, and at times show

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negativistic tendencies. Their appearance cannot help but arouse the physician's sympathy. Two principal complaints are presented: loss of appetite, weight and strength, and various gastrointestinal disturbances, which do not correspond with the history of any of the well-known gastrointestinal diseases. On being questioned as to the cause of the anorexia, most of the patients are unable to express an opinion, or will not do so. Persistent questioning may reveal that in some cases the anorexia directly followed a psychic disturbance. In general, these patients are young; the great majority of them are girls or young women who give a history of cessation of menses of variable duration. The systolic blood pressure is low, and there is an associated slow pulse rate. Loss of weight usually is marked; loss of strength is rather slight, compared to the degree of emaciation present. Complete laboratory examinations give practically negative results. A depressed basal metabolic rate is consistently present. Frequently hypoacidity of the stomach is present, and more frequently, a high total gastric content, denoting lessened gastric motility.

In the group of cases reported I have not considered those patients aged less than thirteen years, observed in the section on pediatrics, nor the group of less than 10 cases in which diagnosis of anorexia nervosa was made prior to 1917.

H. S. Plummer, in 1917, began the investigation of this group in The Mayo Clinic, and in many cases, various studies of metabolism and of chemical changes in the blood were conducted. Since 1917, cases of anorexia nervosa have been studied exhaustively whenever possible, and nothing which would satisfactorily explain the symptoms or physical condition of these patients has been found.

Although anorexia nervosa does not limit itself to the poor, and there is nothing to substantiate the idea that poverty is a factor in the etiology of the disease, the great majority of the cases were among persons whose financial circumstances were not the best. Therefore both treatment and study of the condition have been more or less difficult.

In The Mayo Clinic, during the years reviewed in connection with this article, the diagnosis of anorexia nervosa occurred as follows: 1917, one case; 1918, no cases; 1919, one case; 1920, 4 cases; 1921, 4 cases; 1922, 16 cases; 1923, 7 cases; 1924, 8 cases; 1925, 14 cases; 1926, 16 cases; 1927, 15 cases; 1928, 13 cases, and 1929, 18 cases.

A review of 117 cases might lead one to believe that the occurrence of anorexia nervosa is not at all infrequent; however, considering the yearly registration of patients at The Mayo Clinic, and the fact that this total of 117 cases extends over a period of thirteen years, it is easily seen that the disease is fairly infrequent. Eighty-nine patients in the group studied were females and 28 were males. The ages of the female patients were as follows: 1 patient was aged thirteen years, 11 were aged fourteen and fifteen, 57 were between

the ages of fifteen and twenty-nine, 16 were between thirty and forty, and 4 were aged forty years, or more. The ages of the male patients were: 17 between fifteen and twenty-nine years; 9 between thirty and forty, and 2 were aged forty years, or more.

Eighty-five of the 89 female patients were well within the normal menstrual age limits, and of these, 45, approximately 53 per cent, had amenorrhea. Four patients had passed through the menopause, and in 2 of these the menopause had been artificially established.

Several studies of basal metabolism were made in each case; in view of the element of nervousness or fear of the apparatus, which frequently is responsible for elevated rates, the lower of the first two rates obtained was chosen. These values are shown in Table I. One of the patients, a woman, had been examined prior to coming

TABLE I.—METABOLIC RATE IN CASES OF ANOREXIA NERVOSA.

Males.	Females.	Range of basal metabolic rate.
1	12	0 to -10
6	28	-10 to -20
10	36	-20 to -30
10	11	-30 to -40
1	1	-40 to -42

to the Clinic, and her basal metabolic rate had been well below normal. She had been given a thyroid preparation for seven weeks previous to her examination in the Clinic. At the time of examination here the basal metabolic rate was +1. This case was the only one of the group in which the basal metabolic rate was not below zero. Curschmann, in a review of cases in which the basal metabolic rates varied from normal, concluded that psychoneurosis plays an important part in the depression or elevation of the basal metabolic rate. The depression in metabolism in the cases reported herein had no consistent relationship to the severity of the gastrointestinal symptoms, dryness of the skin and hair, loss of weight or strength, the systolic blood pressure, or the degree of anorexia. Many patients with extreme emaciation, and who were severely ill, however, had basal metabolic rates considerably below normal. Some patients had low basal metabolic rates and complained considerably of gastrointestinal symptoms, but they were not severely ill and the emaciation was not so great as in the cases in which the metabolic rates were higher.

In 47 cases, 40 per cent of the entire group, neurologic and psychiatric examinations were made, to insure against the possible presence of psychosis or of an intracranial lesion. Roentgenograms of the head were taken in many of these cases, but in none was pathologic change evident; the sella turcica was normal in all. As ophthalmologic examinations of the fundus are prerequisites to neurologic examinations in the Clinic, it would seem that gross lesions of the pituitary gland and of structures in its immediate vicinity were

fairly well ruled out. A definite psychologic basis for the anorexia was brought out in only 20 cases. A more exhaustive investigation probably would have disclosed a psychologic basis for the anorexia in many more cases, but in this respect there were two principal difficulties: (1) The diagnosis of anorexia nervosa was not suspected until after the history was recorded in most of the cases, and in many, not until the examination had been completed. (2) The reticence of many of these patients probably would have defeated every effort to elicit a psychologic basis for the anorexia.

In 51 cases, 43 per cent of the entire group studied, dryness of the skin and hair was noted; the condition was present in 39, 43 per cent of the female patients, and in 12, 47 per cent of the male patients.

Gradation of the anorexia present in these cases has been made (Table II), to give the reader some idea of the loss of appetite which occurred. Grade 1 represents moderate but definite anorexia; Grade 4 indicates complete loss of appetite. In many of the latter group of cases it was necessary to institute tubal feeding.

TABLE II.—LOSS OF APPETITE, WEIGHT AND STRENGTH IN ANOREXIA NERVOSA.

Males.	Females.	Quantitative expression of loss of	
		Appetite*	
	2		1
10	12		2
4	26		3
14	49		4
	1	Weight†	Questionable
	3		0
1	6		1 to 10
3	16		10 to 20
10	24		20 to 30
5	18		30 to 40
5	9		40 to 50
1	5		50 to 60
1	2		60 to 70
	2		70 to 80
2	3		90 to 100
	11	Strength*	0
5	30		1
17	33		2
5	12		3
1	3		4

* Grade.

† Pounds.

Gradation of loss of weight also is shown in Table II. In the 2 cases in males indicated as being within the range of 90 to 100 pounds, 1 patient lost 98 pounds and the other 105 pounds. In the 3 cases in females, the loss of weight was, respectively: 98 pounds, 100 pounds, and 101 pounds.

I have also attempted (Table II) to grade the loss of strength. Grade 1 represents a loss of strength apparent to the examining

physician. Patients whose loss of strength was graded 4 were unable to bear their own weight.

TABLE III.—SYSTOLIC BLOOD PRESSURE.

Range, millimeters of mercury.	Cases.
65 to 70	1
70 to 75	3
75 to 80	9
80 to 85	8
85 to 90	22
90 to 95	18
95 to 100	20
100 to 105	10
105 to 110	11
110 to 115	5
115 to 120	7

The systolic blood pressures in this group of patients are given in Table III. The determinations were made during rest, at the time of the metabolic test.

Two cases were not recorded in Table III; in one the readings were 130 systolic and 76 diastolic, and in the other, 140 systolic and 92 diastolic. Although the systolic blood pressure was not consistently low, it can at least be said that the general trend of this group is toward arterial hypotension.

Lusk presented, in chart form, observations on the systolic blood pressure of a man who underwent voluntary starvation over a period of thirty-one days. At the beginning of the fast the systolic blood pressure was found to be at 132 mm. of mercury. During the fast, the systolic blood pressure became gradually depressed, until at the end of the thirty-one days the reading was found to be 100 mm. of mercury.

In relation to the depression of the systolic blood pressure, it might be worth while briefly to review the following case:

CASE I.—A girl, aged fifteen years, presented herself at the Clinic with a complaint of difficulty in swallowing; this trouble had been of short duration. A diagnosis of hysterical dysphagia was made and esophageal bougies were passed. At this time, her weight was 115 pounds, which was her usual weight, and her blood pressure was 118 systolic and 90 diastolic. Eight months later she returned for further examination. She had lost 26 pounds, amenorrhea had been present for four months and the basal metabolic rate was -30 . She complained of vague abdominal discomfort, severe constipation, and mild dysphagia. A diagnosis of anorexia nervosa was made. At the time of this visit to the Clinic her blood pressure was 90 systolic and 60 diastolic. These readings of systolic blood pressure were both determined in the examining room.

So far as had been determined, the pulse pressure and respiratory rate were of no significance. Lusk referred to the fact that in voluntary starvers the temperature does not vary from normal. In the group of cases reviewed in the Clinic, the readings of temperature

correspond to those which would be found in the same number of normal persons.

The pulse rate for each minute, determined at the time of the metabolic tests, was 30 to 40 in 2 cases; 40 to 50 in 22 cases; 50 to 60 in 38 cases; 60 to 70 in 20 cases; 70 to 80 in 22 cases; 80 to 90 in 9 cases, and 90 to 100 in 3 cases. Although there was no consistence, there seems, on the whole, to have been a tendency toward a subnormal pulse rate in the group.

In 12 cases, generalized diseases of the skin were found, and in 12 cases there was brownish discoloration of the skin of the abdomen. In only 3 cases were there both disease of the skin and brownish pigmentation.

In the entire group of 117 cases reviewed, there were but 4 in which the patient did not complain of gastrointestinal disturbances. In 32 cases there was one of an association of several of the following symptoms: distress, gas, nausea, or a sensation of abdominal heaviness, fullness or pressure. One patient had some of the symptoms just named and diarrhea. There was pain with some of the stated symptoms in 12 cases; pain alone in 2 cases; pain with vomiting in 24 cases; pain with vomiting and diarrhea in 5 cases; vomiting and diarrhea in 3 cases, and vomiting alone in 34 cases.

It will be seen, from the foregoing list, that vomiting occurred in 66 cases, 56 per cent of the cases in the entire group. With one exception, the gastrointestinal symptoms were aggravated immediately after ingestion of food. The one exception was the instance of a man who had an associated duodenal ulcer. He had the characteristic symptoms of duodenal ulcer three to four hours after meals, but the vomiting which occurred immediately after he took even small amounts of food was much more distressing to him than his symptoms of ulcer.

In most cases, pain was referred to the epigastrium; however, there were several patients who complained of pain in the lower right quadrant of the abdomen. Several of these patients had undergone appendectomy without obtaining relief. None of the remainder of the group was thought to be suffering from appendicitis. Whenever there was a complaint of diarrhea, examinations of stool and proctoscopic examination were made, as well as roentgenograms of the colon. In many instances constipation to the point of obstipation was a frequent complaint. In the examinations of several of the older patients, roentgenograms of the colon were made in order to exclude the possibility of neoplasm.

Roentgenograms of the stomach were made in 93 cases and analysis of the gastric content in 92. Of the former, 91 cases were reported negative by the roentgenologist; in the other 2, the diagnosis was duodenal ulcer and indeterminate obstruction at the pylorus, respectively. These 2 patients subsequently came to operation. The results of the analyses of gastric content are reported in the

usual way; that is, free hydrochloric acid of 20 would indicate that 10 cc. of filtered gastric content were neutralized by 2 cc. of $\frac{N}{10}$ sodium hydroxid. Free hydrochloric acid was not found in 11 cases; hydrochloric acid was well below 20 in 22 cases and well above 40 in 7 cases. Acidity was normal in 52 cases. In the Clinic, the normal range of free hydrochloric acid is considered to be from 20 to 40.

Although there is nothing consistent in regard to the absence or presence of free hydrochloric acid in these cases, there is a tendency to hypoacidity. Surmount, in an article in which he classified and commented on different types of anorexia, stated that he had found a condition of achlorhydria present in the type of person that is subject to anorexia nervosa. Of the 9 cases of diarrhea, there was associated achlorhydria in 3; the gastric content in the other 6 was well within normal limits of acidity. Examinations of stool were uniformly negative.

Associated diseases were found in the group. Raynaud's disease was present in one case. Addison's disease was suspected, but not proved in 3 cases; one of the patients is dead. Pellagra was found in one and tetany in 2 cases. In 3 cases there was associated pitting edema of the lower extremities.

Thyroidectomy had been previously performed in 2 cases, in one case for simple adenoma and in the other for exophthalmic goiter; in both instances anorexia nervosa developed one year later. Some form of surgical treatment was carried out in 7 cases: in one case, amputation of the breast was performed for carcinoma; in 2 cases, gastroenterostomy was necessary for duodenal ulcer and contracted pyloric ring, respectively; the latter has been referred to as a case of pyloric obstruction. In the 4 remaining cases the operations were minor; that is, dental extraction, making of a window in the maxillary antrum and tonsillectomy.

An attempt was made to cause elevation of the metabolic rate in 85 patients, 73 per cent of the total number included in this study. Sixty-three patients were given desiccated thyroid gland alone, 14 received both desiccated thyroid gland and thyroxin, and 8 were treated with thyroxin, alone. For various reasons no attempt was made to cause elevation of the metabolic rate of the remaining 22 patients: the financial circumstances of some were such as to prevent them from remaining long enough for establishment of dosage; in some the rate was not low enough to warrant the administration of a preparation of thyroid gland; some patients themselves did not consider it worth while to remain for treatment on being informed that cure could not be promised. One patient was given insulin as adjunctive treatment; five units were administered three times daily for several days. There seemed to be some improvement in the patient's appetite, but the treatment was discontinued for lack of definite evidence of value.

Of the group just enumerated, in which treatment with a preparation of thyroid gland was undertaken, 36 patients remained long enough to allow the dosage to be established, and 49 were hospitalized for periods of from ten days to two months.

Two phases of the treatment of anorexia nervosa through the administration of thyroid products are of prime importance: (1) the establishment of the individual dose; (2) the administration of adequate nourishment. The extent to which the metabolic rate may be elevated depends on the amount of nourishment the patient will take; that is to say, if the metabolic rate is elevated and the intake of food is not increased, there will be loss of weight. This is to be guarded against, in view of the fact that when the patient's condition has been such as to necessitate hospitalization, considerable loss of weight has already occurred. It is important that these patients receive the minimal degree of sympathy, but it is of equal importance that they be not antagonized. The problem of nourishment in these cases is difficult enough in the presence of a high degree of empathy between the physician and patient but becomes almost insurmountable in the face of complete lack of the patient's coöperation. Many of these patients may be encouraged to take food in increasing calorie value; others will take only small amounts of food, or none at all, and in this group it may be necessary to pass a stomach tube and keep it in place for some time. Feedings through the tube may be given at frequent intervals, but the intake of food should be increased gradually, for the gastrointestinal symptoms occasionally are exaggerated when the increase is too rapid. Often, following removal of the tube, the patient will be willing to eat; in other cases it may be necessary to replace the tube. The problem of nourishment persists throughout the entire course of treatment and cannot be overestimated.

Lévi reported a few cases of anorexia, emaciation, and low basal metabolic rate, in which the patients were benefited by treatment with thyroid extract. He attributed the condition to thyroid deficiency, but in the group of similar cases herein reported, hypothyroidism has not been considered a causative factor. Bauer, in considering disorders of metabolism due to neurotic conditions, mentioned one case of neurosis with a metabolic rate of -18 , in which very good results were obtained by treating the patient with thyroxin and thyroid extract. Faber, in a publication on anorexia nervosa, reported cure in several cases in which the only treatment was increased intake of food. The basal metabolic rates were not mentioned and evidently treatment with preparations of thyroid gland was not given.

In some of the hospitalized patients, it was possible to cause elevation of the metabolic rate to normal; in some, general improvement in appetite and mental attitude at the time of dismissal was noted. It might be said, here, that the favorable results which we

have seen have not occurred in a short period of time, but over a period of several months and even of several years.

The patients who were treated did not respond uniformly to treatment with preparations of thyroid gland. The rate was elevated to a certain extent in some cases, but it was impossible to cause elevation of the rate to normal on account of complaints of tachycardia, a sense of cardiac oppression, palpitation, headache and generalized aching. In other instances in which the patient responded slowly to administration of thyroid extract, thyroxin was used intravenously for a few doses, after which thyroid extract or thyroxin was given by mouth.

In each of the groups of 85 patients who were given a preparation of thyroid gland to cause elevation of the metabolic rate, the patient was given the individually established dosage and the drug was then continued under the observation of the home physician. The patient was instructed regarding the symptoms which might occur in the event of overdosage, that is, generalized aching, headache, palpitation, tachycardia, loss of weight, and increased nervousness.

Some of the patients returned to the Clinic for observation later, and it was found that the results of treatment with a preparation of thyroid gland were, in general, favorable. There was one group of patients, however, in which the basal metabolic rate was about the same as it had been when the patients were first examined at the Clinic. It is possible that the absence of any increase in metabolic rate could be explained on the basis of a decrease in the intake of food after the patient had returned home, or failure of absorption of the thyroid extract in the gastrointestinal tract. In another group, just the opposite occurred. The basal metabolic rate had increased to above $+15$; in one case it reached $+30$. After these patients had returned home, the appetite and intake of food had markedly increased. In spite of this, these patients had continued the treatment with a preparation of thyroid gland in the dosage which had been determined on at the time of their anorexia and low intake of food. Their return to the Clinic was occasioned by gradual loss in weight, mild tachycardia, and a sensation of all not being well with them. On the whole, these patients appeared to be considerably improved.

It can be said that both the mental and physical improvement is appreciable and in some cases marked, when the metabolism can be maintained near normal without loss of weight. It has been observed that early recognition and treatment of the disease results in a greater degree of improvement over a shorter period of time than is true in cases in which the condition is of long-standing.

In 68 of the 85 cases in which the patient was dismissed with directions to take a preparation of thyroid gland, the subsequent course is known. In 17 cases further information is not obtainable at present. Of the 68 patients whose progress could be followed, 6

apparently returned to normal condition, 24 were markedly improved and 12 received definite benefit. Of the remaining 26, treatment did not effect a change in 14, and 12, 9 of whom are now dead, grew progressively worse. Information is not available relative to 8 of those who are dead. One patient died while in the care of the Clinic; in this case it had been impossible to maintain elevation in metabolic rate although the basal metabolic rate had been raised for a day or so at a time. Death occurred after a period of hospitalization of six weeks. The postmortem examination gave essentially negative results except for the discovery of evidence of bronchial pneumonia.

It must be borne in mind that these data include those relative to patients seen in the Clinic within the last year, and also in part they have been obtained from records of several years ago. In all probability, more exhaustive investigation for information in these cases will reveal additional deaths, and likewise, subsequent data may show the results to be more favorable.

I already have stated that the patients had marked pallor, suggestive of anemia. The records show, however, that the erythrocyte count was well above 4,000,000 per c.mm. in all but five instances; in these five, the lowest erythrocyte count was above 3,700,000.

The mental reaction was not constant. Some patients were definitely psychoneurotic and apprehensive. In a larger group, which included the more advanced cases, the mental reactions were quite similar; these patients were apathetic, reticent, and some showed negativistic tendencies. It is probable that the mental reaction represents an exaggeration of intrinsic traits. In 20 of the cases studied, the onset of anorexia apparently could be traced back to a psychic disturbance. Psychic disturbance may occur in mentally normal persons, or it may be superimposed on mental make-up often described as social inadequacy or biologic inferiority. To substantiate the statement that anorexia nervosa may occur in mentally normal persons, the following case is reported:

CASE II.—A man, aged nineteen years, first came to the Clinic in November, 1920. Eleven months previously he had undergone appendectomy because of an indefinite complaint of pain in the lower right quadrant. The principal complaint at the time of examination at the Clinic was pain in the lower right quadrant and constipation. He stated that four years previously, for a period of two months, he had had attacks occurring every week or ten days, lasting from a few moments to an hour, consisting of right abdominal pain, nausea, and occasional vomiting followed by vertigo, which lasted about one day. He had had four or five of these attacks. Subsequent to this, he began to have constant belching, coming on after eating and occasionally without eating. The constipation grew progressively worse. The appetite became very poor. Two years previous to his examination at the Clinic he noticed that if he would eat more than a certain amount a dull, heavy, epigastric sensation would develop, accompanied by general sensations of languor, and palpitation. The intake of food, therefore, became insufficient to maintain his weight.

Examination revealed an extremely emaciated man. The skin was harsh and dry. He weighed 82 pounds, which was 25 pounds less than his normal weight. The blood pressures were 88 systolic and 62 diastolic, and the pulse rate was 44. The physical features otherwise were negative. Repeatedly, specimens of urine were normal. A complete examination of blood was done; erythrocytes numbered 4,160,000 per c.mm.; the concentration of hemoglobin was 72 per cent; the Wassermann reaction was negative. Analysis of gastric content disclosed total acidity of 60 and free hydrochloric acid of 44, with a total quantity of 75 cc. recovered. Roentgenograms of the head, thorax, stomach and colon gave negative results. Electrocardiograms gave evidence of sinus bradycardia, and the basal metabolic rate was -40 . The treatment with a preparation of thyroid gland was instituted, and the intake of food was increased. This patient remained under observation from December 1, 1920, until January 27, 1921, when he was dismissed to continue treatment with a preparation of thyroid gland at home. The basal metabolic rate was $+1$. There seemed to be slight improvement in his condition.

June 16, 1921, the patient returned to the Clinic. The basal metabolic rate was $+16$. Decided improvement was apparent in the patient's condition; his appetite was good, there was improvement in his facial expression and mental attitude and his only complaint was occasional slight pain in the region of the umbilicus. In spite of the elevated metabolism, the patient had gained 12 pounds. He returned home and discontinued the thyroid treatment.

September 17, 1921, the patient again returned to the Clinic. The basal metabolic rate was -15 . He had gained 15 pounds. He felt fairly well and noticed more improvement in his appetite. He was troubled with a buzzing sound in his ears and a slow pulse, with a sensation of tiredness and drowsiness. His general strength was greatly improved. Treatment with a preparation of thyroid gland was reinstated, and in seven days the basal metabolic rate had been elevated to $+2$. He returned home, again taking a preparation of thyroid gland. In May, 1922, he again consulted the Clinic, in perfect health. His basal metabolic rate was -4 . He was eating well, had no abdominal symptoms, and his nutrition was good. His mental attitude was normal.

Subsequently this patient attended college, and in January, 1927, a letter was received from one of his professors, part of which read, "He has majored with me in zoölogy and I considered him probably the most persistent, capable and enthusiastic student I have ever had. He does high-grade work, not only with me, but in all of his subjects. Recently he was elected to membership in the Phi Beta Kappa fraternity."

Lusk, observing professional starvers, stated that one cannot trace the cause of lowered metabolism in cases of undernutrition to reduction of the mass of body protein, nor to reduction in the mass of body substance itself. It exists in an innate protective mechanism the nature of which one can only dimly surmise. The young men, so nourished, lacked physical strength and lacked a sense of well-being. Also, Lusk said; "Voluntary starvation shows a loss of buoyancy of spirit, a decreased desire to work and a decrease in the actual power of working."

In professional starvers, it was noted that the metabolism did not return to normal soon after ingestion of food. Lusk stated: "The nutritive condition of the body and not the influx of food on the

day previous, determines the height of the metabolism." It has been said in the foregoing paragraphs that the favorable results of treatment did not occur immediately but after several months or longer, in some cases.

The results of postmortem examination in the one case of death that occurred while the patient was under the care of physicians of the Clinic were entirely negative, with the exception of disclosing evidence of bronchial pneumonia, which had been present only two days prior to death. Marshall and Stephens each reported negative results of postmortem examination in cases of anorexia nervosa. Voit, after his experiments in starvation, concluded "Death from starvation is primarily due to loss of substance in organs important to life, but it may also ensue under certain circumstances as a result of deficient nutrition to these organs."

In 7 patients in whom no psychologic basis for the anorexia was brought out, associated conditions were found. One patient suffered from narcolepsy and 6 from encephalitis; 2 of the latter exhibited definite symptoms of Parkinson's disease. One of the patients with Parkinson's disease did not show signs or symptoms of the condition at the time of his first visit to the Clinic, when a diagnosis of anorexia nervosa was made. The patient returned fourteen months later, presenting a typical Parkinsonian syndrome. Since we are just beginning to recognize the various late effects of encephalitis, it is possible that encephalitis may be later shown to have been an important factor in causing the anorexia in some cases of so-called anorexia nervosa.

Assuming that all possible lesions of the thorax and gastrointestinal tract are excluded, the most important conditions to be considered in a differential diagnosis are myxedema, thyroiditis, intracranial lesions, and mental disorders. It is common knowledge that the insane may go on a hunger strike at any time. This fact makes important the exclusion in severe cases of anorexia nervosa of the presence of mental disorders, especially of compulsion-obsessions and psychosis of a depressive nature.

The sequence of events appears to be as follows: A psychic disturbance develops in a number of persons which is directly responsible for, and followed by, loss of appetite. The resulting lessened intake of food finally leads to inanition, which is associated with a process of bringing about a low rate of metabolism. A person with a low metabolic rate requires less nourishment than one with a high rate of metabolism, and in this manner a condition which simulates a vicious circle is brought about. These patients, in the first part of the course of the disease, lose most of their weight. At a certain point the weight becomes more or less stationary. It appears that the depression of the basal metabolic rate acts as somewhat of a protective mechanism, for if the metabolism remained normal, these patients eventually would go on to death, which would occur

much earlier than it actually has occurred in any case. In severe cases of long-standing the least improvement is seen. The fact that the favorable results which we have observed have occurred after considerable time, even though the metabolism and intake of food had been maintained near normal, suggests that other secondary degenerative processes have occurred as a result of the inanition.

In cases of low basal metabolic rate due to hypothyroidism, the clinical picture follows the occurrence of low metabolism. In such cases, although there is some loss of appetite and a decreased requirement for nourishment, the weight is maintained or even increased, as in cases of myxedema. In anorexia nervosa it seems that the opposite occurs; that is, the low basal metabolism follows, rather than precedes, the clinical picture. Although these patients with anorexia nervosa were to some degree intolerant to cold, and a few of them had dry hair and skin, they did not give evidence of symptoms of myxedema, although many of them had metabolic rates much lower than rates frequently found in marked cases of myxedema. In cases of hypothyroidism in which the basal metabolic rate is lower than -20 there is facial edema. This has not been true in any of the cases which were reported as anorexia nervosa, and I have not considered these cases to be hypothyroid states.

I believe that there are other cases of low basal metabolic rate without anorexia which are due to inanition. The number of cases probably is not large. I have recently seen one patient with low rates, who has been eating very little over a period of two years. Two years ago all of his teeth had been extracted, and since that time he has been unable to obtain satisfactory artificial dentures. His complaints were similar to those of cases presented in this paper; namely, mild diarrhea, feeling of fullness and distress, and a dull aching pain in the epigastrium. Complete examination did not reveal organic abnormality except loss of weight. The basal metabolic rate was -29 .

Conclusions. 1. Anorexia nervosa may be said to constitute a definite clinical entity. Briefly, its clinical characteristics are anorexia, inanition, emaciation, various gastrointestinal disturbances, marked nervous manifestations, and low basal metabolic rate. In our experience the condition is not as common as one would expect; 117 cases were so diagnosed in this Clinic in thirteen years.

2. It seems probable that the low basal metabolic rate is the result of inanition.

3. The absence of any demonstrable pathologic change characterizes the condition as a physiologic disorder secondary to a psychic disturbance.

4. The reestablishment of normal intake of calories is the direct goal, and to this end treatment with a preparation of thyroid gland has been proved to be a valuable adjunctive measure.

5. A similar condition due to inanition may be found in some cases in the absence of anorexia.

BIBLIOGRAPHY.

1. Bauer, Julius: Irreführende Gaswechselbefunde, *Klin. Wehnschr.*, 1928, 7, 2090.
2. Curschmann, Hans: Die Stoffwechseluntersuchung in der Diagnostik der Neurosen, *Deutsch. med. Wehnschr.*, 1926, 52, 9.
3. Faber, Knud: Anorexia Nervosa, *Arch. f. Verdauungskr.*, 1926, 37, 17.
4. Gull, W. W.: Anorexia Nervosa (Apepsia Hysterica, Anorexia Hysterica), *Trans. Clin. Soc. London*, 1888, 7, 22.
5. Lasègue, C.: De l'anorexie hystérique, *Arch. gén. de méd.*, 1873, 131, 385.
6. Lecde, C. S.: Anorexia Nervosa: Hypoglycemia or Hypoadrenia, *Northwest Med.*, 1928, 27, 233.
7. Lévi, Léopold: Anorexie mentale et corps thyroïde, *Encéphalé*, October, 1922, p. 507.
8. Lusk, Graham: The Elements of the Science of Nutrition, Philadelphia, W. B. Saunders Company, 4th ed., 1928, p. 764.
9. Marshall, C. F.: A Fatal Case of Anorexia Nervosa, *Lancet*, 1895, i, 149.
10. Stephens, Lockhart: Case of Anorexia Nervosa: Necropsy, *Lancet*, 1895, i, 31.
11. Surmont, H.: Les diverses formes de l'anorexie nerveuse leur diagnostic, *Médecine*, 1920, 1, 603.
12. Voit, E.: Quoted by Lusk.

REVIEWS.

REFLEX ACTION: A STUDY IN THE HISTORY OF PHYSIOLOGICAL PSYCHOLOGY. By FRANKLIN FEARING, PH.D. Pp. 350; 12 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, \$6.50.

It may be regretted that the following sentence does not appear upon the first page instead of near the last.

"From the point of view of physiological psychology we are concerned with the reflex act as a part of the total response pattern of the functioning organism, rather than with the analysis of the functional components of the isolated reflex arc."

To those whose interest in the subject is thus limited, the book gives a perspective of the development of certain trends in psychology arising from the early work on reflexes and a consideration of some recent applications of reflex studies on man to problems in that field. On the other hand, those who look to the analysis of the functional components of reflex arcs for clues to the complex situations which confront the psychologist probably will be disappointed by the author's treatment of his theme. Unfortunately Chapters X and XI are mangled by omission of many pages and misplacement of others, at least in the copy furnished for review.

G. McC.

INFANT NUTRITION. By WILLIAMS MCKIM MARRIOTT, B.S., M.D. Pp. 375; 53 illustrations. St. Louis: C. V. Mosby Company, 1930. Price, \$5.50.

FROM the pen of one whose studies in the laboratory and clinical fields of infant feeding have done much to further that branch of pediatrics, this book has been long expected and awaited.

The first part of the book deals with growth, development, the energy requirements of infants and the metabolism of the food elements, salts and vitamins. This section is handled in a simple, but complete manner, omitting nothing, but avoiding controversial matter. Following this, digestion is discussed and a special chapter is devoted to the stools in infancy and their significance.

One large chapter is devoted to breast feeding and then the subject of artificial feeding of the normal child is considered. The

various types of feeding are discussed and the advantages and disadvantages of each are presented in such a fashion that the particular indications for that food are made very clear.

The various disorders of nutrition such as malnutrition, marasmus, diarrhea, dysentery, celiac disease, vomiting, pyloric stenosis and constipation are fully considered. They are discussed in the light of the newer advances in nutritional physiology. There are complete but not exhaustive chapters on prematurity, rickets, tetany and scurvy.

Two chapters in the book are outstanding. The first is an exposition of the relationship between the common infections of infants and nutritional disease. Much more space is devoted to this important phase of infant feeding than in most other books of this class. The author's pioneer opinions, daily becoming better accepted, are here very clearly stated, especially in the matter of mastoiditis. The other outstanding chapter is on anhydremia, acidosis and alkalosis in which Dr. Alexis F. Hartmann is collaborator.

The book closes with a chapter on pediatric technique, which omits the more obvious procedures, and clearly describes the more difficult ones. Treatment is in many instances explained by illustrative cases, confusing alternatives being avoided, but the reason for each procedure being definitely stated. The Reviewer finds little to criticize about the book; he is a little disappointed that more space is not allotted to the nutrition of the second year and to the subject of anorexia.

Dr. Marriott is to be congratulated upon his simple grammatical construction and lively style which sustains the attention and makes the book easy to read. These virtues are enhanced by its being printed on an unglazed paper in rather large, clear type.

For its crystallization of opinion this book will recommend itself to the pediatricist. As a text it will be found thorough and up to date and will be invaluable to the student and practitioner of medicine. The Reviewer feels that it is one of the most important books in its field.

J. S.

ANATOMISCHE ORGANKRANKHEITEN AUS SEELISCHER URSACHE. By LEOPOLD ALKAN, M.D. Pp. 142. Stuttgart and Leipzig: Hippokrates-Verlag, 1930. Price (unbound), R.M. 9.

THIS volume, which is the fourth of a series intended to present the fruits of clinical research for the benefit of the specialist and the general practitioner, is typographically very attractive; it is printed in heavy-faced Latin characters on excellent paper, opaque and without luster. The latter characteristic is one which American medical publishers might well imitate.

The title may be translated: Organic Visceral Diseases of Psychic Origin. The author adopts the modern dynamic psychology, and on this basis divides the neuroses and the psychoneuroses into transference and narcissistic neuroses. He emphasizes the idea that the mind, or soul, is a function of the whole body (*cf.*, the "heart," "veins" and "bowels" of the Bible), rather than of the brain alone. He believes that there is no sharp line between the functional and the organic, and that visceral neuroses, affecting as they do, the vegetative system, are the precursors of organic changes in the organs. Conversely organic diseases are invariably accompanied by functional and psychic disturbances. Therapy must, therefore, invariably be aimed in three directions, namely: "(1) In the direction of the psyche; (2) in the direction of the vegetative, that is, the sympathetic, parasympathetic and endocrine systems; (3) in the direction of the involved organs." He emphasizes the importance of psychic factors even in conditions usually considered purely organic. In connection with treatment, he alludes to psychoanalysis, but apparently in practice uses the point of view rather than the method. On the basis of these ideas, and with emphasis on the approach from the three angles mentioned, he elaborates the treatment of various circulatory and gastrointestinal neuroses and of their direct physiologic effects and secondary anatomical sequelæ. This book is of special interest at this time because of the present tendency to consider the psychiatric point of view in the diagnosis and treatment not only of neuroses, but also of medical diseases in general.

C. F.

BOOKS RECEIVED.

NEW BOOKS.

The Medical Clinics of North America, Vol. 14, No. 1, University of California Number, July, 1930. Pp. 278; 54 illustrations. Philadelphia: W. B. Saunders Company, 1930.

*Clio Medica, Vol. I, The Beginnings—Egypt and Assyria.** By WARREN B. DAWSON, F.R.S.E. Pp. 86. New York: Paul B. Hoeber, Inc., 1930. Price, \$1.50.

*Clio Medica, Vol. II, Medicine in the British Isles.** By SIR D'ARCY POWER, K.B.E., F.R.C.S. (ENG.). Pp. 84; 1 illustration. New York: Paul B. Hoeber, Inc., 1930. Price, \$1.50.

*Clio Medica, Vol. III, Anatomy.** By GEORGE W. CORNER, M.D. Pp. 82; 8 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$1.50.

* Reviews of titles followed by an asterisk will appear in a later number.

BOOKS RECEIVED

- Hypertension*.* By LESLIE T. GAGER, M.D. Pp. 158. Baltimore: Williams & Wilkins Company, 1930. Price, \$3.00.
- Annals of Roentgenology*, Vol. XI, *The Chest*.* By L. R. SANTE, M.D., F.A.C.P., F.A.C.R. Edited by JAMES T. CASE, M.D. Pp. 561; 246 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$20.00.
- Report of the Fifth International Congress of Military Medicine and Pharmacy*, London, May, 1929, By COMMANDER WILLIAM SEAMAN BAINBRIDGE, M.C.-F., U. S. N. R. Pp. 154; 25 illustrations. Menasha, Wis.: George Banta Publishing Company, 1930.
- Affections of the Eye in General Practice*.* By R. LINDSAY REA, B.Sc., M.D., M.Ch., F.R.C.S. Pp. 155; 40 illustrations. Philadelphia: Lea & Febiger, Inc., 1930. Price, \$3.50.

NEW EDITIONS.

- The Action of Muscles*. By SIR COLIN MACKENZIE, M.D., F.R.C.S., F.R.S. (EDIN.). Pp. 288; 100 illustrations. Second edition. New York: Paul B. Hoeber, Inc., 1930. Price, \$3.50.
- The book deals clearly, if dogmatically, with the aspects of the subject essential to orthopedics. It includes interesting deductions from comparative anatomy. It lays just emphasis upon reciprocal innervation. In the application of this principle to muscles passing over two joints, however, conclusions are drawn with which the Reviewer cannot concur.
- A Textbook for Midwives*. By JOHN S. FAIRBAIRN, M.A., B.M., B.Ch. (OXON.), F.R.C.P. (LOND.), F.R.C.S. (ENG.), MAST. MIDW. SOC. APOTH. (LOND.). Pp. 369; 119 illustrations. Fifth edition. New York: Oxford University Press, 1930. Price, \$8.00.
- This quite comprehensive and up-to-date treatise on obstetrics is intended not alone for pupil midwives of England but for their teachers, medical missionary workers and nurses in Colonial services. The whole subject of obstetrics, normal and abnormal, including operations, and such allied subjects as cancer of the uterus and venereal diseases are covered in such detail as to make an American physician wonder at the mental appetite and digestion of an English midwife. But, as the author remarks, a new type of obstetrician, an educated midwife, is under development, and it is for her that the book is intended. In that case one notes a paucity of illustrations of the more practical procedures she might need to undertake.
- Clinical Features of Heart Disease*. By LEROY CRUMMER, M.D. Pp. 415. Second edition. New York: Paul B. Hoeber, Inc., 1930. Price, \$4.00.
- The author has undoubtedly been a conscientious student of the clinical features of heart disease. His style is clear so that the book is easy to read. Unfortunately, however, it contains so many statements at variance from the views of competent investigators of heart disease that one hesitates to recommend it. In this respect the present edition is not much of an improvement over the first.
- Physical Diagnosis*. By RICHARD C. CABOT, M.D. Pp. 529; 280 illustrations. Tenth edition. New York: William Wood & Co., 1930.
- This well-known book on diagnostic methods and processes is recommended without reservation to practitioners of medicine. One can scarcely fail to benefit greatly from its study. Very little new matter has been added so that those who possess the ninth edition will not need the tenth.

* Reviews of titles followed by an asterisk will appear in a later number.

Diseases of Women. By TEN TEACHERS, under the direction of COMYN'S BERKELEY, M.A., M.D., M.C. (CANTAB.), F.R.C.P. (LOND.), F.R.C.S. (ENG.). Pp. 558; 186 illustrations. Fourth edition. New York: William Wood & Co., 1930. Price, \$6.00.

The present edition has been thoroughly revised and two new authors added to take the place of two who have resigned. The subject matter is brief and direct, such as would appeal to the medical student. It is an excellent manual of gynecology, including sections devoted to urinary and intestinal disorders and the psychologic aspect of pelvic disorders.

Diseases of the Nose, Throat and Ear. By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S. Revised by HOWARD CHARLES BALLENGER, M.D., F.A.C.S. Pp. 1138; 583 illustrations. Sixth edition. Philadelphia: Lea & Febiger, 1930. Price, \$11.00.

This standard work has been thoroughly revamped where changes were indicated. These changes affect principally the chapters devoted to the sinuses, suppurative otitis media and mastoid disease. Dr. Chevalier Jackson and Dr. Gabriel Tucker have contributed a valuable section on endoscopy. The illustrations are clear and abundant, adding much to a work already of great value to the otolaryngologist.

Diseases of the Nose and Throat. By CORNELIUS G. COAKLEY, A.M., M.D., F.A.C.S. Pp. 672; 153 illustrations. Seventh edition. Philadelphia: Lea & Febiger, 1930. Price, \$4.50.

This volume has for its primary purpose the provision of a compact manual of rhinology and laryngology for the student and practitioner. Brevity and clarity are maintained throughout and discussions of moot subjects avoided.

Manual of the Diseases of the Eye. By CHARLES H. MAY, M.D. Pp. 461; 374 illustrations. Thirteenth edition. New York: William Wood & Co., 1930. Price, \$4.00.

The thirteenth edition of this very valuable little book contains an entirely new chapter on the use of the slit lamp. It is certainly one of the best ophthalmic primers in English.

Allergic Diseases: Their Diagnosis and Treatment. By RAY M. BALYEAT, M.A., M.D., F.A.C.P. Pp. 395; 87 illustrations. Third edition. Philadelphia: F. A. Davis Company, 1930. Price, \$5.00.

The appearance of a new edition attests to the continued popularity of this book, primarily written for the layman, but gradually including more and more that will be found useful by the practitioner.

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UNDER THE CHARGE OF
W. S. THAYER, M.D.,
PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,
AND
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Chronic Streptococcal Illnesses.—Many chronic illnesses are attributed to streptococci. These illnesses are usually bizarre, varied and differ in many respects. Some of them, as for example subacute bacterial endocarditis, are definite entities. The same thing applies to rheumatic fever, whereas other diseases are ones that are difficult to label. A person suffers from indefinite ill health; he may have secondary anemia or indefinite dyspepsia. These patients are those who are often found to have areas of focal infection which when removed clear up the general illnesses from which the patient is suffering. There may be also certain chronic local illnesses—surface infections, such as in chronic tonsillitis, chronic bronchitis and chronic sinusitis. PERRY (*Lancet*, London, 1930, p. 1009) notes that in all these conditions streptococci predominate, although the infection may be a mixed one. There is no specificity in the type of the streptococcus producing these lesions. Usually they are of the non-hemolytic or *viridans* group. They may be indifferent streptococci which have the peculiar property of acting as allergizing agents—a property not possessed by certain other microorganisms. As this is so, one is forced from both clinical and experimental data to conclude that the important factor in these chronic streptococcal illnesses is not so much the infecting streptococcus as it is how it enters the host, upon the host itself and the host's previous experience with different streptococci. Streptococci are unfortunately ubiquitous and once a person becomes hypersensitive to these organisms, various manifestations may take place. But little is known about bacterial allergy and immunity. When the difference between complete immunity, in which the patient is safe, and the dangerous state of allergy or hypersensitiveness, perverted immunity is appreciated, then only will practical treatment of these chronic streptococcal illnesses be discovered.

The Rôle of Staphylococci in Food Poisoning.—JORDAN (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 741) writes that the gastrointestinal type of food poisoning is usually considered due to the paratyphoid-enteritidis group of organisms. In fact, some Europeans do not attribute etiologic significance to any other organisms. During the past few years certain food poisoning outbreaks, apparently of bacterial origin, have been studied in his laboratory and thorough bacterial examination failed to disclose any paratyphoid bacilli. This has led the author to the conclusion that other bacteria may be responsible. Fortunately the opportunity occurred to try out this hypothesis. A yellow staphylococcus was apparently the organism responsible for the outbreak of food poisoning in Chicago. The sterile filtrates of 6 staphylococci were tested with human volunteers. From 5 to 10 cc. of sterile broth filtrates, when taken by mouth, produced in a few hours the customary symptoms connoting food poisoning. The staphylococci were of diverse origin. Three were isolated from normal human throats, 1 from a case of septicemia and 2 from food poisoning outbreaks. Twenty-six of the 34 volunteers developed these symptoms, while 11 controls taking the same food remained symptom-free. A second attack was produced by feeding a second portion of the material after a week's interval.

Observations on the Mechanism of Chlorid Retention in Pneumonia.—A heavy postcritical excretion of chlorid in pneumonia is frequently observed. Various explanations have been employed in order to explain this well-known phenomenon. GREENWALD (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 788) attacked the question from an angle which has not previously been tested. He found that in experimental pneumonia there is a very large increase in the excretion of chlorid on the first day, after which the output was much lower than in the control experiments. The author assumes that there is a similarly large excretion of chlorid the first day of pneumonia in man which would account for low concentration of chlorid in the blood and for a part of the marked retention usually observed. If this is true, as much as 8 gm. of sodium chlorid would be lost on the initial day of the disease, explaining why analyses of the tissues of patients dying from pneumonia have failed to show where the presumably retained chlorid was deposited.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Diverticulitis of the Colon.—RANKIN and BROWN (*Surg., Gynec. and Obst.*, 1930, 50, 836) say that diverticulosis is quite prevalent, apparently occurring in about 5 per cent of persons who have symptoms referable to the large bowel, but probably actually occurring in about 1 per cent

of all persons. Diverticulitis probably occurs in about 17 per cent of cases of diverticulosis and in most instances is chronic in its course and subject to exacerbations. The etiology of diverticula is obscure, but they are probably the result of several factors, among them inherent muscular weakness in the wall of the bowel and environmental conditions, obesity and constipation. Diverticulitis probably is the result of improper emptying of the bottle-shaped sacculations with subsequent inflammatory reaction, necrosis and occasional perforation. The relationship of diverticulitis to carcinoma probably is incidental rather than actual. In 227 cases reviewed in this paper as treated at the Mayo Clinic a malignant condition was found associated in 4 only. Diverticulitis occurs almost entirely in persons of middle age who are inclined to be corpulent and who lead sedentary lives. The outstanding symptom of diverticulitis is pain, usually situated in the lower left portion of the abdomen, and is frequently associated with constipation. Change in bowel habit is a confusing factor. Bleeding and tumefaction associated with diverticulitis are common and are usually the result of inflammatory reactions with or without the formation of abscess. In itself it does not indicate associated malignancy. In a definite percentage of cases diverticulitis tends to become complicated. The most common complications are abscess, fistula and perforation. The operation of choice is a graded procedure consisting of drainage with subsequent resection and anastomosis.

The Absorption and Transference of Particulate Material by the Great Omentum.—HIGGINS and BAIN (*Surg., Gynec. and Obst.*, 1930, 50, 851) state that a method is described for the study of absorption by the omentum isolated from all structures within the peritoneum. Studies have been made on the degree of absorption by the isolated omentum from the subcutaneous pouch at frequent intervals, ranging from thirty minutes to forty-eight hours after an injection. Lymphatic vessels within the omentum have not been demonstrated conclusively, and yet absorption from this organ is essentially by way of the lymphatics of the diaphragm and mediastinum. It was not possible to demonstrate either free particles or graphite-like histiocytes in the omental bloodvessels following an injection into the subcutaneous pouch. Following phagocytosis of the graphite particles by active mobile histiocytes, these cells accumulate along the bloodvessels and pass toward the gastric and splenic attachments of the great omentum. The routes of drainage from the distal part of the omentum follow essentially the mesothelial lining of the lesser peritoneal sac. From the gastrocolic ligament, drainage follows around the dorsal surface of the stomach, along the lesser omentum, to the caudate lobe of the liver, and thence along the coronary ligament of the liver and the central tendon of the diaphragm to the anterior mediastinal lymph nodes.

Specificity of Light Action in Tuberculosis.—PHELPS (*J. Bone and Joint Surg.*, 1930, 12, 253) report that definite evidence of specificity of action occurs throughout the spectrum. The wave-length band lying between 320 and 380 millimicrons has been studied both clinically and experimentally. Effects have been obtained which prove this band to be active. The chief effect is an acceleration of the processes of repair

which may or may not be specific for tuberculosis, but which is essential in the retention of function. It is an indirect effect, general rather than local. The band between 320 and 380 millimicrons is found in all sunlight and in carbon arcs of 25 ampères or more, using a carbon of known spectral distribution. Heliotherapy in tuberculosis can be as effectively carried out in sea-level towns as elsewhere. Longer exposures can be given if the erythema and tan-production rays, 300 to 320 millimicrons, are of small quantity or absent. Erythema and tan, therefore, are of no use as a basis of dosage given. Dosage should be measured in all sun therapy and the method of measuring such dosage is outlined. Artificial sources of light containing the band between 320 and 380 millimicrons and comparatively free from the shorter wave lengths are very useful as sun substitutes.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

The Medical Treatment of Spastic Conditions in the Alimentary Canal.—As a result of extensive investigations carried out by himself and by others whom he cites, LOEHR (*München. med. Wchnschr.*, 1929, 76, 1869) finds that a combination of atropin, papaverin and a barbituric acid preparation is the most effective of all medicinal remedies for the relief of spasm both in the alimentary canal and elsewhere, such as in the bronchial tract, the gall bladder, biliary ducts etc. For this purpose he finds a tablet of the following combination to be most satisfactory: atropin sulphate 0.02; papaverin hydrochlorid 0.0005; diallyl barbituric acid 0.025. This tablet should be administered before meals in order to avoid the effects of the digestive secretions upon its components. The dose varies from $\frac{1}{2}$ to 2 tablets repeated three times daily. The drugs comprised in this tablet diminish the hydrochloric acid secretion, allay spasm through both direct action and action upon the nerve endings and diminish pain through a mild general sedative action.

The Failure of Liver Therapy to Control the Cord Symptoms in Pernicious Anemia.—KRAUSE (*Klin. Wchnschr.*, 1929, 8, 2177) reports conflicting evidences from the literature concerning the efficiency of liver diet in the control of the funicular myelitis of pernicious anemia. To these he adds the detailed reports of four of his own patients, all of whom showed a thoroughly satisfactory hematologic response to liver

diet. In none of these four patients however was there any improvement in the spinal cord symptoms. On the contrary, these symptoms either progressed as before the treatment or were apparently somewhat aggravated as a result of the administration of liver. From these and from similar cases reported by others, Krause suggests that the introduction of liver therapy by prolonging life in pernicious anemia may lead to an increased proportion of patients who show severe funicular lesions. He further suggests that the only favorable effect of the liver diet is that upon the blood picture while there is evidence that this diet is associated with some aggravation of the myelitis in certain cases.

Percutaneous Diphtheria Prophylaxis.—In the light of his previous investigations on tetanus toxin and in view of the fact that the injection of diphtheria toxin-antitoxin produces a fairly lasting period of hypersensitiveness to diphtheria, LOEWENSTEIN (*Klin. Wchnschr.*, 1929, 8, 2283) finds, as a result of extensive experimentation upon animals, that a high degree of immunity to diphtheria may be produced by rubbing fairly large doses of active toxin through the epidermis in the form of a salve. The epidermis seems to have the capacity to detoxify such large doses without impairing their antigenic activity. The effectiveness of the inunction of such a salve as diphtheria toxin is proved by immunologic studies on animals as well as on man. When such protective ointment is administered to babies no untoward symptoms result and the blood serum rapidly develops a high antitoxin titer. Not only so, but investigations during epidemics of diphtheria seem to show that infants so treated possess an effective active immunity. The method seems particularly adapted to a large scale of prophylaxis.

The Action of Camphor on the Peripheral Vessels.—HEIMBERGER, in (*Klin. Wchnschr.*, 1929, 8, 2238) points out that the new camphor substitutes which have been so strongly recommended for the treatment of severe cardiac and circulatory failure, have not shown any demonstrable improvement in results over the old camphorated oil. He also emphasizes that, in vasomotor paralysis associated with infectious and toxic processes, neither camphor nor the new camphor preparations have shown any satisfactory results. It is possible however that these agents may stimulate the heart and it has been suggested that they may have a similar stimulant action on the peripheral bloodvessels. With this thought in mind, Heimberger investigated the reactions in the capillaries and arterioles of the fingers in a group of patients to whom 20 per cent camphorated oil, cardiazol, hexeton, coramin and Hoechst's camphor solution were administered hypodermatically directly into the tissues of the finger being studied. These investigations showed conclusively, that none of the agents exerted any specific stimulant action either upon the peripheral vasomotor nerves or directly upon the capillaries or arteriols. Furthermore, the reactivity of the capillaries was not altered. There is no evidence from these experiments indicating that these agents are capable of bringing about any improvement in the peripheral circulation. Since these studies were carried out upon normal individuals, it is impossible to transfer the results directly to those suffering from cardiac or vasomotor failure but there seems to be no good reason for believing that they would act differently in such patients.

The Treatment of Angina Pectoris with Muscle Extract.—SCHWARZ-MANN (*München. med. Wchnschr.*, 1929, 76, 1798) reports a series of 7 illustrative cases out of a much larger series in which he employed an extract made from voluntary muscle for the treatment of angina pectoris. He selected such patients as had very severe angina, the attacks of which recurred at very frequent intervals, being brought on by the slightest effort or by overfilling of the stomach. In the majority of cases the muscle extract was given in doses of from 1 to 2 cc. Prompt relief of the painful seizures followed in most instances after the injection of 1 or 2 doses. The relief lasted from one to three or four days but when the doses were repeated at intervals of two to three days until several successive injections had been made, the relief frequently lasted for weeks. The relief of pain was the most striking response but, in addition, the patients frequently said that they were often completely free from all symptoms of cardiac distress. Such effects were often observed in patients whose symptoms had not been controlled by the usual methods of treatment, including the administration of the nitrites, the xanthins and morphin. In those having demonstrable evidences of coronary and aortic sclerosis excellent results were commonly obtained. The usual dose of the extract was 1 to 2 cc. The author does not offer any explanation of the probable mechanism by which the extract accomplishes these effects.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Relative Prophylactic Value of Convalescent and Immune Adult Serums.—MORALES and MANDRY (*Am. J. Dis. Child.*, 1930, 391, 214) found that the prophylactic use of convalescent measles serum with good results has been reported by various investigators, and that the use of immune adult serum has been encouraged, but they found little evidence in the literature regarding the true value of the serum derived from this source. In this report the authors present data which give adult serum a definite place in the prophylaxis of measles. They found that of 120 children exposed to measles by familial contact and immunized by the use of convalescent serum, 102, or 85 per cent, were completely protected. Fourteen of the 18 attacked in this group developed attenuated measles. Of 132 children exposed to the disease by familial contact, and immunized with doses from 20 to 40 cc. of immune adult serum, 108, or 80.3 per cent, received complete protection and 20 of 26, or 76 per cent, of those attacked developed attenuated measles. Doses of 10 and 15 per cent of adult serum gave complete protection in less than 50 per cent of the persons immunized, but usually resulted in an attenuated form of measles. Of 183 untreated children who were

utilized as controls, living in the same houses with patients who had clinical cases and with treated children, only 34, or 18.6 per cent, failed to contract the disease. Only 2 children had mild reactions among more than 500 who received treatment with serum. It would seem likely that a serious obstacle to the widespread use of convalescent serum will be the objection of some parents to the immunization of their children with blood obtained from strangers. Immune adult serum is readily and universally available, and the technique for obtaining it from adults or children who have had the disease is simple and does not involve any risk. Immune adult measles should be used with greater frequency for the protection of exposed children, especially for debilitated children who would probably die from the disease.

Asthma in Children.—PESHKIN and FINEMAN (*Am. J. Dis. Child.*, 1930, 39, 1240) relate that in 15 children, from three to fifteen years of age, of whom 12 were sensitive and 3 were nonsensitive to protein, the asthma remained severe, persistent and of long duration in spite of treatment according to accepted standards of modern investigation and management. These children had been under observation for an average of two and a fifth years when selected for treatment with the ketogenic diets. No drugs, injections or other therapeutic measures were used. All foods recognized as possible causes of allergy in these patients were eliminated not only from the former diets, but also from the ketogenic diets. An estimation of the amount of food consumed by these children before the beginning of the ketogenic diet showed that they were all living on a high-carbohydrate diet. Average approximate ketogenic-antiketogenic ratio of the home diets ranged from 1 to 2 to 1 to 3. A maintenance diet or one of higher caloric value with a maximum ketogenic ratio of 3 to 1 was reached in all cases except one within three weeks, and after that the level was maintained for periods ranging from four to ten months. At the end of the third week of treatment 14 children, or 93 per cent, showed marked improvement or relief from asthma. Improvement was maintained for two months. After that and up to the tenth month 53 per cent were considered moderately to markedly improved or relieved from asthma. The ketogenic and low-carbohydrate diets alone do not appear to offer much promise of relief from pollen asthma or hay fever. In pollen asthma the administration of pollen treatment in conjunction with the ketogenic diet may prove of value. The results obtained cannot be ascribed to ketosis, as definite improvement or relief from asthma occurred in some children in whom acetone in the urine could not be demonstrated. The use of a maintenance diet or one of higher caloric value with a ketogenic ratio of 3 to 1 in the treatment of a child with chronic asthma who is underweight usually results in an appreciable gain in weight after a period of four months, while in a child who is obese the use of this diet usually results in a loss of weight, in spite of the fact that both types of children have been improved or relieved from asthma. Children with asthma and recurrent eczema on a ketogenic diet showed definite improvement from asthma but aggravation of the eczema. Children who had been free from eczema for several years prior to the institution of the low-carbohydrate high-fat diet did not have a recurrence of the rash in spite of the prolonged ketosis. The estimation of

the requirement in any given case was more easily determined from the formula of Pirquet. The food requirement is determined by multiplying the square of the sitting height in centimeters by the desired number of decinems. Multiplying by $\frac{2}{3}$ the number of calories is obtained. The maintenance diet is calculated at 4.5 decinems and a basal requirement at 3 decinems. The rapid control of asthma or relief from it resulting from the ketogenic diet possibly is brought about by some mechanism which involves a physicochemical change in the cells and blood of the patient, thereby inducing a partially or completely restored physicochemical or allergic balance.

Tuberculosis in Children.—GROSS (*Arch. Pediat.*, 1930, 47, 369) says that tuberculous infection in children is common, while tuberculous disease is not common. Of those infected, a great many, ranging from 50 to 70 per cent, go through life without getting tuberculous disease. Those children that get progressive tuberculous disease in early infancy and childhood usually succumb. Some infants with active tuberculosis do recover. This disease in children is universal and is not confined to any particular sections of the country. Most of the tuberculosis in children belonged to the primary and secondary stages. Physical signs in the lungs are not necessarily the result of tuberculosis, and the clinical history, tuberculin reaction, the fluoroscope and the Roentgen ray must all be considered in arriving at a diagnosis. The reduction of the morbidity and the mortality of tuberculosis is of the utmost importance. The work must begin in childhood.

The Brain-liver Weight Ratio and the Infancy and Childhood History of Epileptics.—WEINGROW (*Arch. Pediat.*, 1930, 47, 392) states that in all types of epileptics the average brain and liver weights vary from those found in the normal. In the idiopathic division, as well as in the symptomatic group without causal postmortem finding related to the epilepsy, and also in the undetermined class, the average brain weight falls below normal in the greatest number of cases. In the nonidiopathic division, with postmortem findings casually related to the epilepsy, the subnormal and the supernormal cases approximate each other. The number of cases in which the liver is below that found in the normal exceeds the number of instances in which this organ showed a normal and supernormal weight in all types of epilepsy described. The greatest percentage of epileptics with liver weights below normal is found in the symptomatic and undetermined groups. The average birth weight of individuals in the essential group does not differ from that in symptomatic division, and the averages of both fall within normal limits. The average age incidences of teething, walking and talking show no appreciable differences in the symptomatic and essential individuals, and their average age range incidence is within that of the normal. The intelligence of the epileptics in the idiopathic division, as judged by the average age at which the individuals commenced and terminated their education and by the grade they reached does not differ from that of the symptomatic division. Measles, pertussis, scarlet fever and diphtheria in the essential present no difference from the symptomatic class of epilepsy. With the brain weights subnormal, normal and hypernormal there seems to be no relationship to

the congenital, developmental or infectious factors mentioned in both the symptomatic and essential classes of epileptics. All groups present evidences of mental impairment as the disease progresses. In the essential epilepsy the mental impairment does not differ markedly from that in the symptomatic group. The brain weight variations have no influence upon the intellectual decline of these individuals in the three types considered.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Lichen Spinulosus Following Intradermal Application of Diphtheria Toxin.—BECKER (*Arch. Dermat. and Syph.*, 1930, 21, 839) stresses the fact that lichen spinulosus is a morphologic term and represents a type of follicular reaction. The acute type may be a form of trichophytid, a form of arsphenamin dermatitis, or due to unknown causes. The chronic varieties are represented by spinulous lichen scrofulosorum, the spinulous type of follicular syphilid and lichen ruber planus. Certain of the chronic forms are recurrent or permanent. The spinulous characteristics may appear as part of another dermatosis. The author has seen such examples in a toxic dermatitis following the administration of gold sodium thiosulphate and in perifollicular seborrheic dermatitis of long-standing. A case is reported in which lichen spinulosus followed a positive Schick reaction in a boy of six years. The author concludes that the follicular apparatus may act collectively as a unit in response to certain noxæ comparable to the epidermal cells in eczema and the superficial vascular system in erythemas, scarlatiniform dermatitis and in urticaria.

Coccidioidal Granuloma: A Clinical and Experimental Review With Case Reports.—JACOBSON (*Arch. Dermat. and Syph.*, 1930, 21, 790) discusses his observations and treatment in 19 cases of coccidioidal granuloma. The previous use of such measures as Roentgen rays, surgery, iodids and intravenous dyes have all be unsatisfactory. The author has employed a colloidal copper and coccidioidin-B with good success except in the acute fulminating type of the disease. This latter type is generally closely associated with the occurrence of face lesions. The author's technique includes deep gluteal injections of the colloidal copper every four to seven days and the cutaneous injection of coccidioidin-B every eight to fourteen days. In selected cases isolated cutaneous lesions may be treated with carbon-dioxid snow. Thirteen cases are reported in detail.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Time of Ovulation.—A rather detailed investigation has been made by OGINO (*Zentralbl. f. Gynec.*, 1930, 54, 464) of Japan into the determination of the time of ovulation and conception with relation to the menstrual cycle. The statistics presented are based upon observation on 118 patients whose ovaries were carefully observed during laparotomy. Of these patients, 81 had a regular menstrual cycle while in the other 37 the periods were irregular. By means of elaborate tabulations he shows that the time of ovulation is a five-day period which comes from twelve to sixteen days before the next menstrual period. By dating the time of ovulation from the next expected period rather than from the last preceding one, a more exact statement can be made, especially in those patients whose menstrual cycles are irregular. In regard to the time of conception, he finds that it is usually during an eight-day period which occurs between the twelfth and nineteenth day preceding the next period, or in other words during the five-day ovulation period and the three days preceding it. During the period of twenty to twenty-four days preceding the menses conception rarely occurs, while during the period of one to eleven days preceding the menses he believes conception is impossible. From a practical standpoint this would mean that a woman becoming married before or during the ovulation time might become pregnant without having any menstrual periods following such marriage. On the other hand if marriage occurs after the time of ovulation it is practically impossible for the woman to become pregnant before she has had a menstrual period. This study indicates that the possibility of impregnation of the human ovum is quickly lost after ovulation.

Prognosis of Uterine Cancer.—As the result of his extensive experience at the Memorial Hospital in New York, HEALY (*N. Y. State J. Med.*, 1930, 30, 191) is of the opinion that the early clinical diagnosis of uterine cancer is the most important factor in the prognosis. Grouping of tumors according to cell type based on Broders' classification is important as a guide to correct treatment and therefore a protection to the patient, especially if the treatment contemplated is surgical. He has found that the prognosis and end-results in uterine cancer vary according to whether operation or radiation therapy is the method employed. With operation, all group 4 cases (Broders' classification)

give uniformly bad results, whereas with efficient radiation therapy the results are surprisingly good, 66 per cent of the favorable cervix cases and 50 per cent of the favorable corpus cases remaining well five or more years. It is absolutely essential that a preliminary study of the histologic structure of the tumor be made from a biopsy specimen or material obtained by curettage in order to determine the kind of therapy that should be employed. While advanced cases which form 80 to 85 per cent of all cases of cervical cancer are entirely beyond the help of surgery, it is interesting that under radiation therapy 23 per cent of his advanced cases were alive at the end of five years. To those who have been following this subject, this figure will appear as probably one of the best yet published in this type of case and shows that progress is certainly being made even though at times such progress seems exceedingly slow.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

Plasmoma of the Conjunctiva in China.—Plasmoma of the conjunctiva being a relatively common disease in China, SOUDAKOFF (*China Med. J.*, 1930, 44, 195) has had an opportunity to observe the disease from its very early stages to very late in its course. Seventeen of these cases were observed both clinically and histopathologically. At the onset it begins clinically as a small growth of the fornix or plica which gradually spreads over the palpebral and bulbar conjunctiva; it may even involve the cornea. Histologically it appears as a diffuse plasma cellular infiltration, beginning either directly beneath the epithelium or separated from that by a strand of connective tissue which is more or less normal. Plasmoma is not a tumor, but rather a reaction to a chronic inflammation caused by some irritant. Thus, the majority of the patients showed trachoma; the author believes that trachomatous toxins act as an irritant. The plasma cellular infiltration prevents the destructive action of the toxins on deeper tissues. Their prolonged action may lead to advanced hyalin-amyloid degeneration of the connective tissue. The treatment recommended by the author is early excision followed by radium irradiation.

Herpes Ophthalmicus Febrilis With Dendritic Keratitis Complicating Therapeutic Malaria.—During a course of therapeutic malaria administered to a patient suffering from cerebral syphilis the cornea of the left eye showed a herpetic eruption, which soon progressed to a definite dendritic type of keratitis; at the same time there was herpes outlining the infratrochlear nerve on the left side of the nose. When admitted to the hospital the patient complained of a visual defect of several years' standing; it was found to be a left superior quadrantic homonymous anopia. The patient was inoculated with tertian malaria and

had six paroxysms. After the fourth he complained of a foreign body in the left eye, which on examination was found to be a circumcorneal injection with lachrymation and photophobia. There was sharp, lancinating pain; the symptoms became worse with each chill. On the third day small vesicles appeared over the temporal margin of the cornea; a pressure bandage was applied and the malaria discontinued. On the sixth day herpetic vesicles appeared along the infratrochlear nerve. Other vesicles appeared to coalesce with those on the cornea, and in a short time there was evident ulceration of the branching or dendritic type. The nasal herpes quickly dried when quinin was given, but the ulceration of the cornea persisted. Atropin sulphate and quartz light therapy did not clear it up. It was found that the recrudescence of the disease occurred a day or two after the administration of neoarsphenamin. As soon as this was stopped there were no more flareups and the corneal clouding diminished markedly. Vision is still partially obstructed, however; there are no changes in the visual fields. EBAUGH and JEFFERSON (*Arch. Neurol. and Psychiat.*, 1929, 22, 1226) state that the absence of other signs of arsenic poisoning throws some doubt on their deduction of the relation of the neoarsphenamin to the herpes. On the other hand, herpes simplex has been known to occur in arsenic poisoning. The condition is important, as it is an indication for immediate cessation of the malarial treatment; it may result in permanent visual defect; relapses may occur during postmalarial, arsenic therapy.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

Further Observations on Dental Caries as a Contributing Factor in Maxillary Sinusitis.—On a previous occasion,¹ Berry estimated that 60 per cent, and conceivably 80 per cent, of patients with paranasal sinus disease would show some form of dental caries in the antral bony floor. To his original series of 152 cases, BERRY (*Arch. Otolaryngol.*, 1930, 11, 55) adds 73 cases of which 59 per cent had a demonstrable abscessed infection of a root of a tooth just below the involved antrum. The author again outlines the technique of ascertaining dental caries in connection with maxillary sinusitis by transillumination and reiterates his plea that the "careful rhinologist must consider gross dental pathology."

The Effect of Camphor, Eucalyptol and Menthol on the Nasal Mucosa.—As reported in a former article (*Arch. Otolaryngol.*, 1927, 6, 112), Fox, learned from a series of experiments on clinical patients and laboratory animals that menthol was more irritating to the nasal mucous membranes than camphor or eucalyptol. In a subsequent publication (*Arch. Otolaryngol.*, 1930, 11, 48) Fox illustrates by photomicrographs the actual anatomic changes encountered in the nasal

¹ Vide retrospect: *AM. J. MED. SCI.*, 1929, 178, 143.

mucous membranes of rabbits sprayed once daily for nine months with liquid petrolatum solutions of menthol, camphor or eucalyptol. The experiments were designed to parallel the usual application of these drugs in practice. All materials for microscopic study were obtained at autopsy. When applied to the nasal mucous membrane of a rabbit for nine months, it was found that, whereas menthol used in dilutions as low as 1 per cent caused some degenerative changes, the same drug in 5 per cent dilutions produced definite destructive changes throughout all layers of the Schneiderian membrane. Deleterious effects were also noted following the similar administration of 5 per cent camphor, 5 per cent eucalyptol and even liquid petrolatum. Since some of the animals in each group exhibited pulmonary abscesses, the author is of the opinion that these abscesses were possibly aspiration phenomena occurring during the intranasal spraying.

Repair in the Paranasal Sinuses of Man Following Removal of the Mucous Membrane Lining.—Sufficient clinical evidence as accumulated in recent years to show that certain persistent infections of the paranasal sinuses necessitate surgical removal of the involved mucosal lining. Moreover, it has been observed that subsequent repair occurs with variable results. Inasmuch as the exact nature of the new tissue has never been determined, SEMENOV and KISTNER (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 322) subjected to histopathologic examination the mucous membranes of human antra from which varying amounts of the mucosa had been removed at former operations. In two instances in which almost one-third of the antral mucous membrane had been removed two years previously, microscopic sections showed the original portion of the lining to consist of such normal histologic structures as: (1) a layer of pseudostratified ciliated columnar epithelium; (2) a superficial spongy layer of areolar connective tissue with large tissue spaces; (3) tuboalveolar mucous and serous glands in the layer of loose connective tissue; (4) an orderly arrangement of branching arteries and arterioles in definite layers, and (5) a definite periosteal layer of compact connective tissue. The repaired portion, on the other hand, consisted (1) of a thick mass of fibrous scar tissue covered for the most part by an indifferent layer of cubical epithelium which was stratified in some places and entirely absent in others; (2) of an irregular vascularization of the scar tissue, and (3) an absence of the usual mucosal architecture, as well as of the glands. Following complete subperiosteal exenteration of the antral mucous membrane it was observed in 2 cases—eight and eighteen months after the primary operations, respectively—that there was a marked thickening of the bony walls and that the antra were lined by a thick, dense layer of scar tissue which was firmly adherent to its subjacent structures and was covered by stratified columnar epithelium when epithelization extended from the nasal mucosa or by stratified squamous epithelium when it extended through an opening in the canine fossa. Abundant regeneration of glands occurred in those cases where the reparative process began from the flap of Schneiderian membrane brought through the fenestrum in the nasoastral wall. This observation is in accord with experimental findings on dogs (Knowlton and McGregor).¹

¹ *Vide* retrospect: *AM. J. MED. SCI.*, 1929, 178, 144.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

Calcification of Intrathoracic Exudates.—Certain observers incline to the theory that tuberculosis is largely responsible for calcified intrathoracic exudates, but there are others who hold that the cause is non-tuberculous. ANDERSON (*Am. J. Roent. and Rad. Therap.*, 1929, 22, 531) reports three cases favoring the claims of the latter group. One was a case of interlobar pleurisy, the second a case of calcified exudate along the left ventricle of the heart and the third a case of pericarditis calculosa. This is the nineteenth recorded case of pericarditis calculosa diagnosed during life.

Ultraviolet Radiation Therapy in Erysipelas.—Presenting data from 91 cases of erysipelas treated by ultraviolet light, UDE (*Radiology*, 1929, 13, 504) advocates the method as universally applicable because it is readily available, requires but one treatment, is devoid of danger, is inexpensive, and the results are comparable to those of any other method. The technique is simple and can be carried out with any ultraviolet lamp. Ude employs a distance of 8 inches. The exposure time varies with the efficiency of the lamp and should represent twice the time required to produce a mild erythema on normal skin. Local applications of magnesium sulphate solution or other substances are not permitted following irradiation.

A Study of the Halogenated Oils Employed in Roentgenology.—For several years iodized oils have been employed to great advantage for the roentgenographic and roentgenoscopic visualization of certain body cavities. The iodized oils, however, are unstable toward heat, light and moisture; the iodine or iodides subsequently always liberated in the body may, over long periods of time, cause toxemia, irritation, or iodism; their cost is considerable, and their viscosity is so high that they are frequently ill suited for the particular purpose. Accordingly, TABERN, HANSEN, VOLWILER and CRANDALL (*Radiology*, 1930, 14, 364) have undertaken the development and study of brominized oils and esters as substitutes for the iodine mixtures. Two products have been found to possess the most desirable properties. The first was 33 per cent brominized olive oil esters (viscosity, seven seconds) and the second a mixture of 85 per cent brominized olive oil and 15 per cent of brominized olive esters (viscosity, one hundred and twenty seconds). For filling nasal accessory sinuses the brominized olive esters are preferable; filling is rapid and complete and the time of drainage is

reduced by many hours. The ester product is also superior for visualization of the seminal vesicles and has been used successfully for pyelography. It was introduced into the uterus and Fallopian tubes, and little pressure was necessary, but the tubal shadows were less distinct than with oils of higher viscosity. For visualization of the bronchial system the second mixture is preferable. The brominized oils and esters are more stable than the iodized oils, have controllable viscosities without loss of radiopacity, are economical to manufacture and use, low in toxicity and, of course, cannot cause iodism.

The Roentgenologic Manifestations of Intracranial Disease.—In order of their importance the various roentgenologic signs of intracranial disease are grouped by CAMP (*Radiology*, 1929, 13, 484) as follows: (1) Calcification within the lesion itself; (2) localized changes in the bone, such as destruction, proliferation or both; (3) changes in the sella turcica; (4) changes in the bone from increased intracranial pressure; (5) displacement of the pineal shadow; (6) air in or about the lesion; (7) increased vascularity of bone. Lesions that may exhibit calcification include tumors, hematomas, tubercles, cysts, old abscesses, old meningeal lesions, encephalitis, sclerotic arteries and aneurysm. Such calcification requires distinction from the calcification which often occurs normally in the pineal gland, choroid plexus and Pacchionian bodies. The bones of the skull overlying a contiguous tumor may exhibit locally the changes of destruction, proliferation or both. Most often the change consists of thinning of the internal table. Hyperostosis may occur, especially in association with parasagittal tumors and those that arise from the temporofrontal meninges. Lesions causing deformity of the sella turcica include benign and malignant tumors of the pituitary gland, extrasellar tumors giving rise to increased intracranial pressure, and disease of the sphenoid bone. Displacement of the shadow of the pineal gland is valuable in the diagnosis and localization of intracranial tumors. Increased vascularity of the bone is likely to accompany angiomatous tumors of the cortex. The value of the foregoing signs has been variously appraised. Crouse from a review of the literature estimated that 8 per cent of the lesions of the brain can be diagnosed from the roentgenogram. Dandy computed that 15 to 20 per cent can be localized. Sosman, reviewing the main groups of tumors, was able to identify the tumor by means of the Roentgen ray alone in 37 per cent.

Interpretation of Gastric Symptoms.—The conclusions drawn from a study of 3000 consecutive patients requiring a gastrointestinal examination are presented by DWYER and BLACKFORD (*Radiology*, 1930, 14, 38). It is well known that the majority of patients who complain of gastric symptoms do not have organic disease and this is corroborated by the present series. Only 15 per cent of the patients had organic lesions of the stomach or duodenum to account for the symptoms. Duodenal ulcer was found in 8.1 per cent and was the most common organic finding in the stomach or duodenum. Gastric ulcer was only a fifth as common as duodenal ulcer. Cancer was found in 3.6 per cent of the patients who had gastric symptoms; 80 per cent of the cancers apparently originated in a resectable area of the stomach. Disease of

the gall bladder was the most frequent cause of the symptoms, and was regarded as responsible for the dyspepsia in 21.3 per cent. In 59 per cent of all cases the cause of the dyspepsia was not due either to functional or organic conditions in the stomach, duodenum or gall bladder.

Infraclavicular Foci of Infiltration as Evidence of Incipient Tuberculosis in Young Adults.—During the last eight years ASSMANN (*Radiology*, 1930, 14, 93) has encountered what he believes to be a characteristic type of pulmonary lesion in the early stages of tuberculosis of the lungs, particularly in young adults. The lesion, as seen with the Roentgen ray, consists as an isolated rounded focus of varying density, usually situated just below the clavicle, in the lateral part of the pulmonary field, more rarely in the upper portion of the lower lobe. Such a lesion is usually sharply circumscribed and definitely contrasted, but it may have little density and show a gradual transition into the normal pulmonary field. It is of fundamental importance to understand that, in contradiction of the generally accepted idea that tuberculosis of the lungs nearly always begins in the apices, the type of lesion described, the infraclavicular focus, is associated with absolutely normal apices. From this focus a general tuberculosis may develop, but with timely treatment a favorable prognosis may be given.

Radium in the Treatment of Disease with Subcutaneous Mucosal Hemorrhages.—Five cases are reported by HOFFMAN (*Radiology*, 1930, 14, 136), comprising 2 of umbilical hemorrhage, 2 of purpura hemorrhagica and one of hemorrhage after circumcision in all of which radium treatment of the spleen was given. Save in one of the cases of umbilical hemorrhage, bleeding was stopped and in both cases of purpura hemorrhagica the disease has not recurred. The author concludes that radium offers a new and valuable aid in the treatment of hemorrhagic diseases of the newborn, as well as in simple purpura hemorrhagica. In hemophilia radium will help in controlling the severe hemorrhages without other medication. He warns that if the total erythrocyte count is below 1,000,000 this method must be used very cautiously because of the hemolytic action of gamma rays, and preliminary transfusions should be given to bring the blood count above that level.

The Roentgen Treatment of Morbus Basedowii.—HOLZKNECHT (*Radiology*, 1930, 14, 139) points out that since 1904 it has been known that morbus basedowii can be cured by Roentgen ray treatment, about 60 per cent of cases showing cure and about 20 per cent improvement to a greater or less degree. He concedes that a very acute case of the disease should be operated on because of the quick relief which ensues. Cases not responding to Roentgen ray therapy and those with signs of tracheal compression by a large nodular struma should also be operated on. But there is no reason at all for giving up local treatment of the thyroid, and there is no basis whatsoever for resorting to general skin treatment with grenz rays, as advocated in certain quarters. As to the rays producing adhesions which render subsequent operation difficult, statistics prove that adhesions, if found, were already there before treatment, and that they occur just as often in untreated as in treated cases.

Roentgen Ray Diagnosis and Therapy of Thyroid Disease.—The Roentgen ray, properly applied, is a safe therapeutic agent in thyroid disease, according to REMER and BELDEN (*Radiology*, 1930, 14, 145). Certain cases of toxic goiter should be given the benefit of irradiation for at least four treatments, continuing it if improvement is noted, and referring the case to surgery if no improvement occurs. Radiation does not increase the difficulty of subsequent operation. Radiation before operation renders a patient a better surgical risk. The danger of hypothyroidism is negligible. The basal metabolism test is an important adjunct and the treatment should be governed by it. Severe cases should be hospitalized and a period of rest obtained before treatment is begun and after the first one or two exposures.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

The Distribution of Nonelectrolytes Between the Blood and the Cerebrospinal Fluid.—COCKRILL (*J. Nerv. and Ment. Dis.*, 1930, 71, 443) presents a discussion of the theories of the nature of the cerebrospinal fluid. He selects urea distribution between the blood and cerebrospinal fluid as being of the greatest significance because of the accuracy of determination and the fact that there is no reason to believe that urea is either consumed or produced by any part of the nervous system or adjoining tissues, and because of its ready diffusibility and solubility. He calls attention to the fact that the cerebrospinal fluid water consistently contains less urea than that of the blood plasma. He believes that the discrepancy would be even greater if the water content of the two fluids were taken into consideration by the investigators. Experiments on cats showed that with an accumulation of urea in the blood the urea concentration of the cerebrospinal fluid increased at approximately the same rate, the discrepancy in distribution remaining the same. Dialysis experiments *in vitro* indicated that under these conditions there was a tendency for the urea concentration to equalize between the blood plasma and cerebrospinal fluid. He considered these results as evidence against the view that the cerebrospinal fluid is produced solely by ultrafiltration of the plasma.

Huntington's Chorea Without Choreiform Movements.—CURRAN (*J. Neurol. and Psychopathol.*, 1929-30, 10, 305) presents a case of Huntington's chorea exhibiting the typical hereditary characteristics, and occurring in several members of the family, in only one of which were

choreiform movements present. Dysarthria was the only motor symptom manifest in the majority of the cases, but marked mental deterioration was common in all. Two members of the family had been diagnosed as cases of general paresis, and the case presented had points of similarity with this disease. It is pointed out that the complete absence of motor symptoms does not necessarily negative the diagnosis of the disease. Stress is placed on the distinctive heredity and the differential diagnosis.

A Case of Decerebrate Rigidity With Autopsy.—EPSTEIN and YAKOVLEV (*J. Neurol. and Psychopathol.*, 1929-1930, 10, 295) reveals a case of decerebrate rigidity first observed in a child at the age of two years and seven months, and under observation until death, at the age of eight years and three months. The case in history and physical findings is typical of cerebral infantile tetraplegia of congenital or immediately postpartum origin. The neurologic findings were typical of decerebrate rigidity with the tonic neck reflex of Magnus and de Kleijn, extensor rigidity, pseudoaffective reactions and tonic fits. Pathologic study resulted in the anatomic diagnosis of microcephaly and microgyria, cerebral aplasia with absence of corpus callosum, aplasia of the cerebellum and the basal ganglia, degeneration of the thalamus, diffuse gliosis and corticospinal tract degeneration.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Contribution to the Study of the Sympathetic Nerves of the Appendix: The Musculonervous Complex of the Submucosa.—MASSON (*Am. J. Path.*, 1930, 6, 217), while studying nerve proliferation in the appendicular mucosa and the origin of carcinoid tumors, acquired the idea of a submucous musculonervous complex. This article deals fully with the latter mechanism as studied in different types of appendices. The so-called "complex" is made up of fine bundles of muscle tissue, which separate themselves from muscularis mucosæ and pass into submucosa, where they anastomose with similar fibrillar bundles, passing off obliquely from the inner circular muscle of the same sector of appendix. These muscle elements are very intimately associated with the nerves of Meissner, which are always present between the muscle network. The most typical structure is noted in the submucosa of appendices of the newborn. This "normal" type is maintained in healthy adult

appendices. But in appendices showing the results of repeated crises, characterized by extreme diminution of lymph nodules, thickened walls and narrowed lumen, the muscle bundles of the complex are hypertrophied, as are the elements of Meissner's plexus. Accompanying this change the walls of the vessels, including the intima, are thickened. Various gradations of hypertrophy and hyperplasia are noted, the most extreme presenting small neuromata throughout the mucosa as well as hypertrophy of both elements of the complex within the submucosa. The significance of the musculonervous complex described is obscure to the author. In the discussion it is suggested that in the appendix two groups of nerves are found, the argentaffin group and the myenteric group.

Spontaneous Tuberculosis in the Guinea Pig.—GRIFFITH (*J. Path. and Bact.*, 1930, 33, 153) has found that spontaneous tuberculosis occurs but rarely in the guinea pig. Of 7 strains examined by him from cases of spontaneous tuberculosis, 6 were bovine and 1 human. He further reports what apparently are the first recorded examples of spontaneous avian tuberculosis in guinea pigs. The lesions produced by the avian bacilli differ from those usually found when mammalian strains are inhaled, in that the tracheobronchial glands are enlarged, but show no fibrotic thickening and contain purulent rather than caseous material.

The Local Effect of the Injection of Gases Into the Subcutaneous Tissues.—While gases have been previously injected into the body, WRIGHT (*Am. J. Path.*, 1930, 6, 87) is apparently the first to report on the result of subcutaneous injections of gases, particular attention being paid to the local tissue reactions. The studies were conducted in close association with studies upon tuberculosis where large numbers of monocytes and epitheloid cells were noted as the chief tissue reaction. A similar reaction was observed following the injection of yellow phosphorus. These experiments were carried out to determine whether or not this reaction was due to a common chemical etiology or if it was purely physical and nonspecific. Small amounts of sterile oxygen, nitrogen and carbon dioxide were introduced at different intervals, depending upon the rates of absorption and sections from the altered areas studied. The results showed that, following an immediate acute reaction, there were produced in the injected tissues large numbers of monocytes, modified monocytes, epitheloid cells and giant cells. The reaction, due to nonspecific causes is similar to that seen in tuberculosis and occasional histologic structures closely resembling tubercles were observed. The authors believe that the monocytes present arise locally "from some type of fixed connective-tissue cell," and that, in turn, the epitheloid and giant cells originate from the monocytes. The cellular analyses are described and portrayed in detail.

Osteogenesis Imperfecta Congenita.—WEBER (*Arch. Path.*, 1930, 9, 984) reports a case of osteogenesis imperfecta in which the triad of symptoms necessary, according to von Recklinghausen, are fulfilled. He attempts in his analysis of the case to determine at what stage in the development of bone the changes peculiar to osteogenesis imperfecta

arise. He uses as a basis, stages in bone development outlined by himself in a previous article. He finds that while the formation of mesenchymal tissue, osteoid tissue and chondroid tissue proceeds along normal lines, the entire bone-producing system is arrested in the "nucleus" stage, the stage in which the intercellular substance becomes calcified, forming nuclei for the latter deposition of lamellar bone. The bone present consists of "fiber" bone of an inferior quality. True lamellar bone is completely lacking, and osteoclasts are entirely absent except in the region of callus formation.

Antibacterial Action in Cultures of *Penicillium*, With Special Reference to Their Use in Isolation of *Bacillus Influenzæ*.—FLEMING (*Brit. J. Exper. Path.*, 1929, 10, 226) describes the action of a substance, which he calls penicillin, contained in the filtrate of a broth culture of a strain of a penicillium. This substance inhibits the growth of the Gram-positive cocci of the mouth (staphylococcus, streptococcus and pneumococcus), while the other oral organisms are practically unaffected, especially *Bacillus influenzae*. By planting throat swabs on chocolate-agar plates, and smearing 6 to 8 drops of penicillin over half of the plate, the author has easily isolated this organism, even though it was present amid multitudes of staphylococci and streptococci. In a more recent article (*Brit. J. Exper. Path.*, 1930, 11, 127), in conjunction with MACLEAN, the author records having found *Bacillus influenzae* in cultures made from the gums of 30 normal individuals by means of penicillin.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. MCCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

The Rôle of the Vaccination Dressing in the Production of Post-vaccinal Tetanus.—ARMSTRONG (*Pub. Health Rep.*, 1929, 44, 1871) arrives at the following conclusions: (1) Tetanus as a complication of vaccination against smallpox is confined, as far as we are aware, to primary "takes" in which some type of dressing was strapped to the vaccination site. (2) Evidence is produced which indicates that in postvaccinal tetanus the specific organism gains entrance to the vaccination through an accidental infection from extraneous sources. (3) Evidence is produced which indicates that a deep implantation of *Bacillus tetani* in the devitalized components of the "take" is necessary before postvaccinal tetanus will develop. (4) A dressing strapped to a

cutaneous vaccination permits this deep implantation of organisms by producing severe "takes," and by retaining exudate therefrom at the vaccination site. (5) Injection methods of vaccination such as the intracutaneous technique are suitable methods for the experimental production of postvaccinal tetanus and would seem to be, from the standpoint of this complication, a potentially dangerous method for human use. (6) The freedom of openly treated cutaneous vaccinations from the complication is explained by the continued wiping and ventilating action occasioned when the arm is moved within the sleeve or under the bed clothes. This light friction keeps the vesicle dry and firm, and thus either prevents or promptly wipes away any exudate which may appear. (7) A small, superficial implantation of the virus, as recommended in the multiple pressure technique advocated by Surgeon J. P. Leake, and the abandonment of dressings fixed to the vaccination site will eliminate tetanus as a complication of vaccination. If a dressing is deemed advisable for any reason, the objectionable feature of the *fixed* covering can be avoided by pinning a few layers of gauze to the inside of a loose-fitting sleeve.

Experimental Epidemiology of Tuberculosis.—Normal guinea pigs confined with tuberculous cage mates were found by Perla to acquire tuberculosis of alimentary origin, characterized by a marked involvement of the mesenteric and cervical lymph nodes. Guinea pigs confined in the same room with tuberculous animals but not in the same cage acquired a disease of respiratory type, characterized by extensive lesions of the lungs and of the tracheobronchial lymph nodes. The incidence of the disease increased with the intensity and duration of the exposure. His work did not, however, show conclusively the effect of crowding upon the incidence of "contact" tuberculosis, because the intensity of exposure in his experiments was not the same in each degree of crowding. Perla's studies have been continued by LURIE (*J. Exper. Med.*, 1930, 51, 729). In judging these experiments it must be borne in mind that the experimental epidemiology of tuberculosis entails greater difficulties than a similar study of a more acutely fatal disease. The laborious nature of the experiments, extending over long periods of time, the chronicity of the disease, the relatively low incidence of tuberculosis acquired naturally by guinea pigs precludes the rapid demonstration of facts. The author found that if normal guinea pigs are confined with an equal number of tuberculous cage mates the incidence of "contact" tuberculosis is increased by crowding. This is probably due largely to an increase in the amount of tubercle bacilli available in the more crowded cages, although no constant relationship could be established between the intensity of the exposure and the incidence of tuberculosis acquired by contagion. Other factors must be determined. If guinea pigs are inoculated intraperitoneally with a given quantity of human tubercle bacilli, and distributed in different degrees of crowding, the duration of survival is shortened in the more crowded animals, and the incidence of chronic types of tuberculosis is greater among the less crowded animals. Guinea pigs living in the same room but not in the same cage with tuberculous animals acquire tuberculosis, characterized by a chronic course, a marked involvement of the lungs, often with cavity formation and a massive tuberculosis of the tracheobronchial

nodes; the mesenteric and cervical nodes are slightly or not at all affected. The route of infection in these guinea pigs is almost always the respiratory tract. Of 103 guinea pigs exposed for a period of up to thirty-two months, 15, or 14.5 per cent, developed tuberculosis. The shortest period of exposure leading to fatal tuberculosis was eight months. The incidence of this tuberculosis acquired by air-borne contagion increases with the duration and intensity of the exposure up to a certain point. A large percentage of the guinea pigs weathered a continuous exposure to the tubercle bacillus for thirty-two months without becoming tuberculous. This may be due to an innate natural resistance against tuberculosis, or to an acquired immunity resulting from the continuous exposure to the contagion. If normal guinea pigs are confined with tuberculous cage mates in cages where the food becomes contaminated with the excreta, laden with tubercle bacilli, of the inoculated animals, the incidence of acquired tuberculosis among them is greater than among guinea pigs similarly exposed in cages where this mode of infection is largely eliminated. The disease acquired in the first type of cage is largely of enteric origin and is chronic in type. The disease acquired in the second type of cage is of respiratory origin and has a more acute course. In tuberculosis of guinea pigs acquired by contact with tuberculous guinea pigs under conditions permitting the entrance of tubercle bacilli both by way of the alimentary and of the respiratory tracts, the type of lesion produced depends upon the relative intensity of exposure to infection by one or the other channel. With the gradual elimination of exposure to alimentary infection tuberculosis is more and more completely engrafted through the respiratory route. With the gradual increase in the intensity of exposure to alimentary infection, the disease becomes more and more completely enteric in origin. Some evidence is presented that the engrafting of tuberculosis by way of the alimentary route inhibits the development of respiratory disease.

A Study of Rural School Ventilation: The School Ventilation Study in Cattaraugus County, N. Y., 1926-27.—DUFFIELD (*Pub. Health Rep.*, 1929, 44, 2383) states that there are in New York State about 8000 one- and two-room schools with about 150,000 pupils while in the whole country about 3,500,000 pupils attend such schools. The conclusions are as follows: (1) Rural schools heated by furnaces and jacketed stoves were more generally overheated than rooms with ordinary stoves. (2) Lateral temperature distribution was very good in the rooms heated by furnaces but very uneven in stove-heated schools. The average difference between temperatures on desk tops in different parts of the room exceeded 10° F. in nearly half the rooms, and in individual instances the observed difference was as great as 30° and 40° F. (3) Vertical differences in temperature were great, that is, floor temperatures were low—half the rooms averaging below 60° with one extreme record of 31°—and ceiling temperatures (in the rooms in which such observations were made) high—often over 90°, and in two rooms averaging over 100°—in rooms where no provision was made for the artificial circulation of air. (4) In general, one and two room rural schools, such as those observed in Cattaraugus County, appear to be highly unsatisfactory from the standpoint of heating and ventilation. They

are subject to gross overheating on the one hand and to serious chilling on the other, and show wide horizontal and vertical differences in the temperatures existing simultaneously in different parts of the same room. (During the Spring of 1928 three schools were provided with insulating material in varying degrees. The heating equipment in these and a few other schools was also replaced or altered and later it will be possible to report on the results that can be obtained under improved conditions in this type of school.) (5) Absenteeism in one- and two-room schools of Cattaraugus County ranged from 6 to 37.8 per cent, with an average of 14.1 per cent, which is twice as high as the average rates observed in Syracuse and New York City. The mean rates of the middle half of the rooms in the Cattaraugus County study fell between 10.7 and 17.5 per cent. (6) Absenteeism reported due to respiratory illness in the Cattaraugus County rural schools varied from 1.2 to 9.7 per cent of the total pupil sessions, with a mean of 4.7 per cent, which was twice as high as the corresponding rate for the current Syracuse study and four times that found in the New York City studies of the former commission. The middle half of the reported rates of respiratory illness absenteeism in the rural schools of Cattaraugus County fell between 2.3 and 6.4 per cent of the total pupil sessions. (7) In general, the prevalence of respiratory illness showed an inverse relationship to outdoor temperatures, that is, the incidence of respiratory illness was greater during the cold months of the year. In the absence of other factors, however, low temperature itself did not appear to be directly associated with increased respiratory illness. (8) During periods of low temperature, deviations from the general trend of the incidence of respiratory illness varied with the fluctuations in precipitation, the maximum effect occurring in the week following that which had an excess of precipitation, with the exception of the last week of the study.

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ORIGINAL ARTICLES.

CLINICAL AND PATHOLOGICAL STUDIES ON SO-CALLED
TUBULAR NEPHRITIS (NEPHROSIS).

By S. BURT WOLBACH,

PROFESSOR OF PATHOLOGY, HARVARD UNIVERSITY,

AND

KENNETH D. BLACKFAN,

PROFESSOR OF PEDIATRICS, BOSTON, MASS.

(From the Children's and Infants' Hospitals, Boston.)

MANY writers, believing that the histopathology of the kidney can be indicated with some degree of accuracy, when the history of onset and the distinctive clinical symptoms are correlated with the laboratory data, classify acute nephritis in children as: (1) Acute glomerular nephritis; (2) acute tubular nephritis; (3) acute "mixed" nephritis. This classification includes the common forms of acute nephritis seen in childhood and is supported by much pathologic evidence.

The clinical and laboratory data suggested as criteria for so separating the three different forms are as follows: (1) *Acute glomerular nephritis*: (a) A history of an acute infection antedating the onset; (b) hematuria; (c) visible or nonpitting edema; (d) increased arterial tension; (e) increased nonprotein nitrogen in the blood; (f) cerebral symptoms (uremia); (g) recovery. (2) *Acute tubular nephritis*: (a) Insidious onset without any antedating infection; (b) albuminuria, high specific gravity and lipoid bodies, casts and leukocytes, *no erythrocytes*; (c) marked pitting edema and ascites; (d) low plasma protein; (e) normal nonprotein nitrogen; (f)

normal arterial tension; (g) remissions and exacerbations; (h) termination with secondary infection. (3) *Acute "mixed" form* (in this group are placed those cases in which the onset, clinical course and laboratory data vary in one or more respects from characteristic features of 1 or 2). Examples of this are an insidious onset, with marked edema and albuminuria and elevated blood pressure, low plasma protein and normal nonprotein nitrogen or an onset following an acute infection, with a marked pitting edema, normal blood pressure, low plasma protein and alternating periods in which the urine shows an excessive albuminuria or *erythrocytes*, even *gross blood*.

As is generally known, the kidneys in the glomerular form are somewhat enlarged and the glomeruli are prominent. Practically all of the glomeruli are more or less involved. The tubules being an essential part of the renal unit, show changes which in all probability are secondary to, and to a large extent, dependent on the glomerular injury. The degree of fibrosis or scarring is directly proportional to the severity of the injury. When severe and continuous or recurrent, the process passes on to the development of the secondarily contracted kidney of adult life, the probable sequences being loss of renal tissue below functional adequacy, consequent hypertension and finally the development of the arteriolar degenerations characteristic of the primarily contracted kidney or so-called vascular nephritis. In acute tubular nephritis the notable changes in the kidneys are their increased size, the obscuring of normal markings and the presence of edema, pallor and opacity. Degenerative lesions are the characteristic feature. The proximal and distal convoluted tubules are the seat of diffuse degenerative changes with fat formation and there is cellular response only to such necrosis of tubules as may be present. The glomeruli are but slightly if at all involved, even when the process has continued for many weeks. In the mixed form of nephritis, the kidneys show lesions representative of both types.

Within recent years there has been much discussion concerning tubular nephritis, or nephrosis as termed by many authorities. Most of the contributions have come from adult clinics where the complexities surrounding the etiology and pathology are notably confusing. The most recent work on acute tubular nephritis in children has been reported by Davison and Salinger.¹ They present the clinical and laboratory findings with detailed pathologic studies in 4 patients. During the past five years, in children with acute nephritis, we have seen 21 cases which, according to the clinical and laboratory data, fulfill the requirements for the diagnosis of acute tubular nephritis. Ten of these patients died and necropsy was obtained in 8 patients.

The purpose of this communication is to report a clinical and pathologic study of 8 fatal cases of acute tubular nephritis in

ANALYSIS OF DATA OF EIGHT CASES OF ACUTE TUBULAR NEPHRITIS.

Case No.	Age at death.	Duration.	Remissions.	Clinical diagnosis.	Exceptions.	Terminal events.	Ratio to normal kidney weight.	Histology.
I	3½ yrs.	2½ yrs.	6	Acute tubular nephritis	Occasional R.B.C. in urine	Hemolytic streptococcus peritonitis	236 104	Cicatrices; hyalin droplets; mitoses
II	3 yrs., 11 mos.	6 mos.	2	Acute tubular nephritis	Initial high B.P.; Nervous origin?	Hemolytic streptococcus peritonitis and pleuritis	333 104	Cicatrices; hyalin droplets
III	6 yrs.	4 mos.	2	Acute tubular nephritis	Typical case	Hemolytic streptococcus peritonitis	200 132	Cicatrices; necrosis and regeneration
IV	1 yr., 11 mos.	6 mos.	3	Acute tubular nephritis	Slight increase in B.P.; slight increase in N.P.N., 56 mg.	Hemolytic streptococcus septicemia	259 93	Cicatrices; hyalin to necrosis; streptococcus; emboli in glomerulus
V	2 yrs., 3 mos.	3 mos.	0	Acute tubular nephritis	Onset with acute infection; coryza and fever	Acute streptococcus peritonitis and pleuritis	128 96	Granular degeneration to rare necrotic cell; fat
VI	2 yrs., 2 mos.	5 wks.	0	Acute tubular nephritis	Onset with acute infection; coryza, vomiting, fever, rapid course	Pneumococcus pleuritis and peritonitis	92 93	Granular degeneration and hyalin droplets
VII	3 yrs., 8 mos.	?	0?	Acute tubular nephritis	Typical case	Streptococcus (?) peritonitis	176 114	Hyalin to complete necrosis
VIII	1 yr.	8 mos.	2	Glomerular tubular nephritis	Terminal high B.P. 120 to 170 100 105	Pneumococcus septicemia; Streptococcus viridans peritonitis	138 88	Granular degeneration; fat

children, with a view of ascertaining the accuracy with which a pathologic diagnosis can be determined from a consideration of the clinical and laboratory data. The essential clinical and laboratory features have been reviewed and from them an opinion as to the underlying pathologic process has been expressed. The accuracy of the clinical diagnosis has then been checked with the histologic findings.

The criteria taken as indications for degenerative lesions in the uriniferous tubules, without glomerular or interstitial changes, have been mentioned above. Any deviations from the characteristic findings have been regarded as exceptions to the rule and suggest that glomerular lesions with or without interstitial changes exist.

The character of the material of this report is outlined in the table on page 453. In the column of kidney weights the upper figure is the combined weight of the kidneys; the lower figure is the average of normal weight of both kidneys for corresponding age.

If the before-mentioned clinical and laboratory criteria are rigidly followed in establishing the diagnosis of acute tubular nephritis, only 2 of the 8 cases can properly belong to this form of nephritis. They are Case III and Case VII. It is true, the other 6 cases show only slight or minor departures from the so-called pathognomonic signs, such as: Case I, the finding occasionally of a few erythrocytes, microscopically in the urine; Case II, an initial high blood pressure which subsequently became normal; Case IV, a slight increase of blood pressure and a slightly increased nonprotein nitrogen; Case V, an onset of edema and albuminuria with an acute infection; Case VI, an onset with an acute infection and with rapidly progressing widespread terminal infection; Case VIII, an onset with vomiting and edema at fourteen months, again at sixteen months, at twenty-one months, edema and albuminuria and increasing blood pressure. These minor variations from the criteria characterizing tubular nephritis were considered by us to be of importance as possibly indicating the presence of kidney lesions not repairable by simple regeneration of tubular epithelium. However, we have not been able to find significant differences in the pathology of the 8 cases and have discarded the hope of giving prognostic value to the type of information presented.

Case Histories. CASE I.—The patient, N. G. (Hospital No. 10109), was under observation from the onset of albuminuria and edema at nineteen months of age until he died of generalized peritonitis, when three and a half years of age. When first seen he had been ill for two weeks with generalized edema, and albuminuria. Insofar as could be ascertained, the edema was not preceded by an acute infection, and physical examination revealed no evidence of a local or general infectious process. The temperature was 105° F. on admission but remained normal throughout his stay in the hospital (four months) with one exception, when it rose to 103° F. for five days. No explanation was found for the fever at that time. During his stay in the hospital there were two periods in which the edema practically dis-

appeared; the urinary output increased and there was a lessened albuminuria. In the first period he lost $5\frac{1}{2}$ pounds in six weeks; in the second period he lost 5 pounds in eight weeks. At the end of this period he was discharged much improved. Albumin and cellular elements, however, continued to be found in the urine. Various measures to influence the edema were tried without striking results. He remained at home eight months. In this interval, the course was characterized by remissions and recurrences of edema. The edema became excessive during an attack of mumps, and the daily urinary output dropped from an average of 560 to 620 cc. to 120 to 150 cc. The urine continued to contain albumin and cellular elements. On the second admission (one year after onset) he showed generalized edema and albuminuria over a period of three months. No evidence of local or generalized infection could be found. There was one remission in which he lost 5 pounds in two weeks. Thereafter the edema remained stationary until, without apparent cause, it entirely disappeared. The effects of high-protein diet were tried as on the former admission without noteworthy results. There was a lessened amount of albumin and fewer cellular elements in the urine when he was again discharged. Following this discharge his general health and appearance remained good but there was always a slight trace of albumin in the urine. During the winter he had diphtheria. The edema and albuminuria returned, but gradually disappeared. He was admitted for the third time (nearly one year after second admission but almost exactly two years after the original onset) because of a recurrence of the edema and albuminuria. These symptoms had recurred two weeks before and were definitely associated with an acute respiratory infection and an acute parotitis. The temperature fluctuated between 98° F. and 100° F. The patient was observed in the hospital over a period of four months during which various therapeutic measures were tried. Calcium chlorid resulted in a temporary loss of weight but repetition of the course of treatment had no effect. Ammonium chlorid was likewise without benefit. The protein content of the diet was increased; the child continued to gain weight and theocin and caffein were given. These measures had no effect on the edema. In 6 days the weight increased from 36 pounds to $38\frac{1}{2}$ pounds. Caffein was omitted and the patient was given diuretin. The edema continued to increase; three days later the weight reached 40 pounds and was then stationary. The protein in the diet was increased to 60 gm. and subsequently to 70 gm. This change in diet seemed to have some effect on the edema. He was discharged free from edema three weeks later weighing $31\frac{1}{2}$ pounds. Albumin and cellular elements remained present in the urine. A few days after discharge, although he was kept on the high-protein diet, the urinary output began to diminish and the edema to recur. He was returned to the hospital (fourth admission) for this reason. The temperature varied between 99° F. and 102° F. for ten days. It then rose rapidly and remained about 102° F. to 104° F. until he died, twelve days later. With the terminal rise in temperature, the edema increased markedly and the patient complained of pain in the region of the right kidney. Tenderness became marked in this region as well as over the abdomen. With the question of a perinephritic abscess or a generalized peritonitis in mind, an exploratory incision was made over the right kidney. Pus was not found. The kidney capsule was stripped (Edebohl's operation) without any benefit to the patient. He rapidly became worse and died a few days later. *Non-hemolytic streptococcus* was recovered from the peritoneal fluid.

Laboratory Data. First Admission. The white blood cells were 24,900 per c.mm., 75 per cent were polymorphonuclear in type. *Urine:* Specific gravity, 1020 to 1032; albumin (0.5 to 1 gm. per cent); granular and cellular casts; many white blood cells; an occasional red blood cell; N.P.N., 30 mg. per 100 cc.

Phenolsulphonephthalein test, 75 per cent (two and a half hours). *Plasma protein*, 5.75 per cent. *Fixation test* normal.

Second admission. Urine: Specific gravity, 1020 to 1035; albumin, 4.8 gm. per cent; hyalin and granular casts and white blood cells. White blood cells 16,000 to 40,000 (60 per cent polymorphonuclears); N.P.N., 28 mg. per 100 cc.; chlorids, 533; cholesterol, 397; *serum protein*, 5.23; blood pressure, 100/60; *phenolsulphonephthalein*, 40 per cent.

Third Admission. Urine: Specific gravity 1010 to 1020; albumin, 3 gm. per cent; many hyalin and granular casts and white blood cells; *blood pressure*, 110/60 to 65/40.

Summary (by Dr. Blackfan before the autopsy). The diagnosis of acute tubular nephritis was made by the appearance of albuminuria and edema without an antecedent infection and without evidences of a focus of infection, by exacerbations, sometimes but not always initiated by an intercurrent infection and by remissions, at which times the patient was free from symptoms, together with the termination by hemolytic streptococcus peritonitis. The clinical findings when correlated with the laboratory data which showed a normal nonprotein nitrogen, a low serum protein, an albuminuria, normal phenolsulphonephthalein and a normal blood pressure, support the impression that the outstanding lesions found would be degenerative changes in the tubules. The finding of a few red blood cells in the urine from time to time may mean slight changes in the glomeruli.

Autopsy (A-24-115). Four and a half hours postmortem, restricted to the abdomen.

The condition of the heart and lungs was not ascertained.

There was an acute peritonitis which proved to be due to an hemolytic streptococcus. The spleen showed irrelevant changes.

The gastrointestinal tract showed no lesions.

The pancreas was normal in gross and upon microscopic examination.

The liver weighed 420 gm. It showed a fine yellowish mottling. The color as a whole was pale and cut surfaces were cloudy in appearance. The gall bladder and bile passages were normal. Microscopically there was a moderate degree of fatty infiltration in the form of large drops at the peripheries of the lobules. The liver cells throughout were reduced in size and showed marked acidophilic staining, fine vacuolization and there was much granular debris between liver columns and sinusoids. There was much separation of liver cells so that the columns appeared disorganized. No necroses.

The adrenals were small; microscopically they showed congestion and a marked diminution of cortical lipid.

The bladder and genitalia were normal.

The kidneys: The right weighed 116 gm., the left 120 gm. They were enlarged, pale, succulent with obscured markings. The cortex measured 0.5 cm. to 0.7 cm. in depth and was finely mottled with opaque yellowish lines and dots. The glomeruli were visible with difficulty as red points.

Microscopic Examination. The glomeruli were essentially normal. A few showed an increase of cells in the capillaries, polymorphonuclear leukocytes and mononuclear cells presumably from the endothelium; attributed to the effects of the streptococcus peritonitis.

The convoluted tubules throughout the many sections taken from both kidneys showed striking change. The proximal convoluted tubules were dilated and occasionally infolded, and usually contained much granular detritus and circular reticulum. The epithelial cells were either swollen or diminished in size, the cytoplasm granular and finely vacuolated and occasionally with colloid droplets. Some swollen granular cells seemed to be discharging portions of their cytoplasm into the lumen of the tubule; elsewhere the cells were much reduced in size. The nuclei in general were

normal and cells showing evidence of actual necroses were rare. Mitotic figures were occasionally found. The distal convoluted tubules showed similar but less striking changes. The Henle's loops showed slight or doubtful changes. The collecting tubules showed finely vacuolated cells. The Henle tubules, distal convoluted and collecting tubules contained many deeply staining casts of hyalin material. In the cortex were a few minute cicatrices, most of them of compact fibrous tissue. Some, however, contained many lymphoid and plasma cells and rarely one contained a residuum of necrotic tubule. Occasionally such cicatrices were in contact with fibrosed glomeruli. These cicatrices we interpreted as the result of repair following complete necrosis of tubules.

Fat stains showed considerable amounts of fat in the convoluted and collecting tubules in the form of small droplets. Most of the fat stained deep red with Scharlach R, and pink or red with Nile-blue sulphate.

The important lesions of these kidneys were in the convoluted tubules. The slight glomerular changes were those usually with an acute streptococcus infection. In spite of the clinical evidence of long standing, recurrent renal disturbance, the microscopic study has revealed only a rare minute cicatrix and lesions which were degenerative in type and which can be produced experimentally in a comparatively few days.

CASE II.—C. P., aged three and a half years (Hospital No. 100113) was observed over a period of six months. He was admitted to the hospital five weeks after an insidious onset with edema, ascites and albuminuria. After three months he was discharged, much improved. He remained apparently well for two weeks, when following an acute respiratory infection, he was returned with the edema and albuminuria as advanced as at the previous entry. Two months later he was exposed to measles and was sent to the contagious division. The edema subsided and he remained free from symptoms for one month, then he was returned to the hospital because of recurrence of the edema, albuminuria, fever and abdominal pain. He died three days later with an hemolytic streptococcus peritonitis.

Laboratory Data. *Urine:* Specific gravity, 1025; large amount of albumin; no red blood cells; hyalin and granular casts. *Blood:* 25,000 white blood cells, 68 per cent polymorphonuclear; *plasma protein*, 3 to 5 per cent; N.P.N., 30 mg.; blood pressure at the first admission was 150/100, remaining high for several days, then varying around 90/60 mm.

Summary (by Dr. Blackfan before the autopsy). One would hesitate in this case to infer from the initial blood pressure alone at the first admission, especially with the subsequent normal blood pressure findings, that this finding indicated glomerular involvement. The element of nervous influence on blood pressure in children always needs to be considered. The clinical course and laboratory data would support the belief that the outstanding histological changes would be in the kidney tubules.

Autopsy (A-27-74). Two hours postmortem. The immediate cause of death was acute peritonitis and pleuritis due to an hemolytic streptococcus.

Heart: Weight, 75 gm. It showed no relevant or important lesions.

Lungs: Weight, right, 160 gm.; left, 115 gm. Both lungs showed acute bronchitis and bronchopneumonia grossly and microscopically. The pneumonic process proved to be of the infiltrating type with peribronchitis and interstitial pneumonitis, with numerous recent thrombi in bloodvessels. Many streptococci were present in the vessel walls and in the thrombi.

Gastrointestinal tract: The gastrointestinal tract was negative grossly and microscopically.

Pancreas: Negative in gross and microscopically.

Liver: Weight, 925 gm. The gross appearance was not remarkable. Microscopically there was a moderate infiltration of peripheries of lobules

with fat in the form of large drops. In addition, throughout the liver the cells were finely vacuolated and the cytoplasm filled with deeply eosin-staining granules with occasional cells containing a basic staining reticulum. There was much débris between the liver columns and sinusoids, the latter contained an excess of polymorphonuclear leukocytes and large mononuclear phagocytes. These appearances were interpreted as acute changes, presumably due to streptococcus toxins and to be characterized as cloudy swelling or acute parenchymatous degeneration.

Adrenal glands: Grossly negative; microscopically they showed a marked diminution of cortical lipid and occasional foam cells. The medulla was normal.

Bladder and genitalia: Normal.

Aorta showed a few minute atheromatous patches in the ascending portion.

Organs of the neck: Normal.

Brain: Weight, 1200 gm. Markedly edematous.

Kidneys: Weight, right, 158 gm.; left, 175 gm. They were enlarged, soft, succulent, pale yellowish-brown. On section the parenchyma everts from the capsule. The markings were obscured. The cortex measured 1 cm. in width, flecked with minute opaque-yellow areas and demarcated by a band a few millimeters wide at the base of the pyramids of opaque yellow. The pelves and ureters showed no lesions and were apparently normal.

Microscopically, there were lesions of two distinctly different periods, one represented by numerous linear cicatrices containing atrophic tubules and infiltrated with lymphoid and plasma cells. In the proximity of the cicatrices were occasional fibrosed or fibrosing glomeruli. Some of the atrophic tubules contained polymorphonuclear leukocytes and the appearance suggested involvement of the kidney secondary to an infection of the pelvis. The pelvic epithelium was intact, but beneath it was a moderate lymphoid and plasma-cell infiltration. It is probable that this late lesion was secondary to severe degenerative lesions of the tubules.

The second type of lesion was very striking and uniformly distributed; a degeneration of the epithelium of the convoluted and ascending Henle tubules. The convoluted tubules were markedly dilated, oftentimes the epithelium was infolded. The epithelium in most of the tubules was greatly swollen, finely vacuolated and filled with eosin-staining granules. Occasionally there was a regenerating cell, rarely a completely necrotic cell invaded by leukocytes. There were numerous pyknotic nuclei. The distal convoluted tubules and ascending Henle tubules frequently showed rather large densely staining hyalin globules basally situated. Also there was evidence of edema of the interstitial tissues throughout the kidney. There were many deeply staining casts of hyalin material in tubules of various types. The glomeruli were practically normal. A few contained migrating leukocytes, probably the first evidence of recent damage due to the streptococcus infection. Scharlach R stains showed much less fat than the gross appearance of the kidney suggested. Tubules of all types showed a moderate amount of fat in the epithelial cells. In some groups of convoluted tubules it was excessive in amount. Such tubules were usually those with flattened epithelium. There was a small amount of fat fairly uniformly distributed in the ascending Henle tubules and in the collecting tubules. This kidney summarizes as follows:

1. Evidence of a healed destructive lesion, presumably repair after destruction of tubules.

2. Severe tubular nephritis with intact glomeruli.

As in Case I, it is impossible to correlate the apparently recent injury of the tubules and the history of six months' illness. Both middle ears con-

tained pus in which were long-chained streptococci. The drums were dull colored and thickened.

CASE III.—W. C., aged five and a half years (Hospital No. 77165) was admitted to the hospital on November 17, 1924. Two months previously the mother noticed that his eyes were swollen and that he was irritable and had anorexia. The physician found albumin, casts and leukocytes in the urine. Insofar as could be ascertained no acute infection preceded the edema and albuminuria. The examination was negative except for the generalized edema and ascites.

Course in the Hospital. Temperature varied between 98° and 100° F. during his stay in the hospital, with the exception of two separate occasions when it rose to 103° and 101° F. No cause was determined for these rises which lasted each time less than twenty-four hours. *Edema:* He weighed 42 pounds on admission. He gained 2 pounds in weight during the first week of his stay in the hospital and then remained at this weight for the following two weeks. During this time he was given calcium chlorid over a period of three days. This was followed by small doses of sodium bicarbonate (1 gm. twice daily). These measures did not influence the edema nor the urinary output. The edema, however, was materially influenced, as shown by decrease in weight and urinary output, when the dose of sodium bicarbonate was increased to "1 gm. four times a day." *Intake and output* rose from 1000/780 to 1000/1300. The weight fell from 43½ to 38 pounds. The tonsils and adenoids were removed and he was discharged after having been under observation about six weeks. There was no edema, the very slightest trace of albumin, and there were no cellular elements in the urine.

Subsequent Course. Three days after his return home, he developed an acute respiratory infection. This was followed by an increase in the edema. He remained in bed, but was returned to the hospital after a month—February 11, 1925, inasmuch as the edema increased and the urinary output diminished (1200/290).

Examination on return revealed nothing abnormal except the marked edema. The temperature on admission varied between 99 and 101° F., and six days after admission rose to 105° F. At that time peritonitis was suspected because of abdominal pain. On account of rapidly increasing fever and abdominal distention, an exploratory operation seemed advisable. peritonitis was found.

Laboratory Data (first admission). *Urine:* Specific gravity, 1008 to 1012; albumin ++. The sediment contained an occasional granular and hyalin cast. *Blood:* Erythrocytes, 5,000,000; hemoglobin, 90 per cent; white blood cells, 17,000 (45 per cent polymorphonuclears); phthalein test, 55 per cent; N.P.N., 47 mg. per 100 cc.

Laboratory Data (second admission). The urine showed a large amount of albumin with a few hyalin and granular casts. N.P.N. was 29.2. The blood pressure remained around 95/60. The culture from the purulent fluid showed nonhemolytic streptococcus. The patient died.

Summary (by Dr. Blackfan before autopsy). The diagnosis of acute tubular nephritis was made by the insidious onset without an antecedent infection and edema, the remissions and the terminal infection of a non-hemolytic streptococcus peritonitis. The urine contained albumin, hyalin and granular casts, white blood cells and no red blood cells, the nonprotein nitrogen and phenolsulphonephthalein test were normal as well as the blood pressure. Therefore the correlation between the clinical course and the laboratory data would suggest histologic changes involving the kidney tubules without manifestations in the glomeruli.

Autopsy (A-25-24). The postmortem examination, made one hour after death, was restricted to an inspection of the abdomen through the surgical incision and removal of the kidneys for histologic study.

There was a diffuse fibrinopurulent peritonitis. An hemolytic streptococcus was cultivated from the exudate.

The liver was large, firm, low in position. The spleen enlarged, soft and pulpy. The kidneys weighed each 100 gm. They were large, pale, mottled with yellow, and unusually soft. On section the parenchyma was soft, succulent and bulged from the capsule. The cortices measured 1 cm. in width. The color was opaque, yellowish, mottled with red throughout the cortices. The glomeruli were prominent as red dots. The pyramids were injected, their apices deep red in color. The capsules stripped with slight difficulty and left slightly granular surfaces. The pelves and ureters were normal.

Microscopic Description. Twenty-two blocks from both kidneys showed identical appearances. Severe tubular degeneration and occasionally necrosis of tubules with practically intact glomeruli characterized the kidneys. The lesions affected chiefly the convoluted tubules and the ascending loops of Henle's tubules. The epithelium of the tubules exhibited all degrees of damage from cloudy swelling to complete necrosis. The proximal convoluted tubules showed large vacuoles basally situated in the cells in great numbers. These were filled with fat which stained red with Scharlach R and pink with Nile-blue sulphate. With polarized light most of the fat proved to be isotropic, only occasional droplets proved doubly refractive. While the fat vacuolization was heaviest in the convoluted tubules, actual necrosis of their cells was rare. The distal convoluted tubules, ascending Henle tubules showed greater swelling and granulation of cells and there were many systems of tubules with nearly every nucleus in a pyknotic condition. There were a few tubules filled with desquamated necrotic cells, invaded by polymorphonuclear leukocytes and surrounded by lymphoid and plasma cells and polymorphonuclear leukocytes. In convoluted tubules there were occasional cells containing deeply stained acidophilic hyalin coagula somewhat similar to the picture found in corrosive sublimate poisoning. Rarely were mitotic figures found in the tubular epithelium. The glomeruli in general were intact. A few only showed an increase of cells in the capillaries, rarely one with hyalin thickening of the cement substance of the capillary walls. Scattered through both kidneys were very small cicatrices, rarely larger than could be accounted for by the disappearance of a single tubule, most of these cicatrices contained lymphoid and plasma cells and could be explained as the consequence of the reactions following necrosis of tubules—an explanation which probably accounted for the change in occasional glomeruli. Tubules of all varieties contained material in sequence of cast formation, granular débris and circular reticulum in the proximal convoluted tubules, granular and deeply staining hyalin casts in Henle loops and distal convoluted tubules. With polarized light, fatty acid crystals and doubly refractive globules were found in the casts in frozen sections.

CASE IV.—S. L. (Hospital No. 10983), a male, aged twenty months, was regarded as a normal infant until the onset of the present illness. This began insidiously three months before admission to the hospital with edema and suppression of urine. No acute infection, so far as could be ascertained, preceded the onset of the edema. The examination revealed an extremely edematous infant with free fluid in the peritoneal cavity and slightly elevated blood pressure.

Course in the Hospital. Urinary output—during the first twenty-four hours in the hospital the patient voided but once. Thereafter the urinary output appeared in fair proportion to the intake of fluid. The temperature ranged around 99° to 103° F. for twelve days, after which it remained normal for six weeks. It became elevated then, varying from 98° to 104° F.

for seven days. Following an interval of normal temperature for twelve days, it rose to 104° F. where it remained until the end.

Infection. Every effort to find a focus of infection was unsuccessful until three days before last febrile period, when an abscess developed in the region of the left scapula. This was opened and drained. Its point of origin was not determined. *Streptococcus hemolyticus* was cultured from the pus. In so far as could be determined by roentgenogram, there were no evidences of sinus infection. *Weight:* The patient weighed 32 pounds 10 ounces on admission. At no time was he entirely free from edema. There were three periods in which the weight and, therefore, the edema decreased materially. The first period followed the administration of magnesium sulphate, 50 per cent solution, 32 to 45 gm. daily. He lost 7 pounds in two weeks, (32.10 to 24.6 pounds). The second period followed the administration of ammonium sulphate. He lost 5 pounds in fifteen days (34.4 to 29.14 pounds). The third period followed the terminal fever which continued for four days. He lost 1 pound 4 ounces (29 to 27.12 pounds).

Albumin. During the administration of magnesium sulphate by mouth, with the rapid lessening of the edema, the albumin appeared (qualitatively estimated) to be less in amount and there were fewer formed elements in the urine. Throughout the course of the illness the quantitative amount of albumin rose from 4.8 gm. per liter to 7 gm. The *blood pressure* fell from 105/70 to 90/55 during the rapid loss in weight. *Temperature:* The weight and amount of albumin were not influenced by the fever except at the terminus when there was a rapid loss of weight.

Laboratory Data. *Urine:* Marked amount of albumin, many hyalin and granular casts and many leukocytes; no erythrocytes. *Phenolphthalein* 40 per cent in two hours (intravenous); N.P.N., 55 mg.; *serum protein* (venous blood), 5.8 per cent; *albumin*, 7 gm. per liter; white blood cells, 19,000 (50 per cent polymorphonuclears). The blood pressure was 108/70 on admission.

Summary (by Dr. Blackfan before the autopsy). The onset with generalized edema and albuminuria with remissions and exacerbations continuing over a period of six months terminating fatally with an hemolytic streptococcus septicemia when correlated with the presence of 7 mg. of albumin in the urine, a normal phenolphthalein excretion and a low serum protein, would lead one to believe that the chief histologic changes would be found in the renal tubules. The exceptions which might point to glomerular involvement were the slightly raised blood pressure on admission (108/70 as to the normal for the age 80/40) and the slight increase of the total nonprotein nitrogen (56 mg.).

Autopsy (A-24-40, one hour postmortem). Blood not examined. There was generalized edema, hydrothorax and ascites. The immediate cause of death was septicemia (hemolytic streptococcus) presumably secondary to the scapula abscess.

The *heart* weighed 69 gm. Microscopically it showed a moderate interstitial edema.

Lungs. The left weighed 82 gm., the right 98 gm. Both were crepitant and were normal in appearance except for congestion of the lower lobes. The trachea and larger bronchi were normal. Microscopically the lungs were remarkable for the many thrombi in bloodvessels of all sizes. In a few arteries and veins there were organizing thrombi. In many small arteries and veins there were recent thrombi and in the capillaries of alveolar walls there were great numbers of recently formed thrombi, these were both mural and occluding. The former were often composed of platelets and fibrin, the latter of fibrin in coarse strands or in fused hyalin masses. In the capillaries fused red blood corpuscles acted as thrombi free

and within phagocytic cells. In and adjacent to the thrombi in all locations were polymorphonuclear leukocytes and mononuclear phagocytes in varying numbers. The latter often contained pairs and chains of micrococci (Giemsa stain) and in a few instances there were masses of streptococci adherent to the intima of the vessel walls. Large portions of the many sections taken for study were bloodless, the capillaries in the alveolar wall being either thrombosed or packed with large mononuclear cells (phagocytes).

The *spleen* weighed 100 gm. Microscopically it showed collections of phagocytic cells in the centers of the follicles and in the pulp. The splenic veins and sinuses contained a remarkably large number of recent thrombi in composition like those in the lung and occasionally accompanied by streptococci.

Pancreas. Normal.

The *liver* was enlarged. It extended 7.5 cm. below the costal margin, 8.5 cm. below the tip of the ensiform cartilage.

Microscopically, it showed numerous focal necroses and a diffuse degeneration of the liver cells accompanied by a general infiltration with polymorphonuclear leukocytes. In places the continuity of the liver columns was disrupted giving a picture reminiscent of the liver of spirochetal jaundice. The liver cells were shrunken, the cytoplasm of many stained deeply with eosin, most of the cells contained basic staining reticulum and were often vacuolated. The nuclei for the most part appeared viable. In the sinusoids were numerous fibrin thrombi and many mononuclear phagocytes often enclosing polymorphonuclear leukocytes. The bile ducts were normal.

Adrenal Gland. Normal in gross and microscopically. There was considerable lipid vacuolization of the cortical cells.

Kidneys. Left weighed 139 gm., the right 120 gm., were markedly enlarged, pale (light pink), soft, succulent. On incision the parenchyma everted from the capsule, which stripped easily. The markings of the section were obscured, cortex pale, glomeruli visible with difficulty as colorless points, the pyramids injected, the pelves and ureters normal.

Microscopically, the outstanding feature was severe and uniformly distributed degeneration of the epithelium of the convoluted and Henle tubules. Fat stains showed very little fat in the form of fine droplets almost exclusively in the distal convoluted tubules. By stains and polarized light this fat proved to be neutral fat. The tubular epithelium was everywhere swollen and granular and the lumina filled with circular reticulum and granular detritus and in places seemed to be discharging cytoplasm into the lumina in the form of budlike processes. In many places the degeneration was more severe and the cells were filled with colloid drops or reduced to narrow granular fringes. Actual death of cells was evidenced frequently by pyknotic nuclei and there were scattered tubules with completely desquamated epithelium, invaded and surrounded by leukocytes. This account applies to the convoluted and ascending Henle tubules. Densely stained hyalin casts were abundant in tubules of all types. The glomeruli were mostly normal. Numerous ones, however, contained small hyalin thrombi in the capillaries or fibrin thrombi in the arterioles, accompanying this there was a cellular response on the part of polymorphonuclear leukocytes and endothelium. In addition a few glomeruli showed the presence of polymorphonuclear leukocytes and hyalin thickening of the capillary walls without demonstrable thrombi. Rarely there was a glomerulus with proliferation of the capsular epithelium and complete occlusion of the tuft capillaries by mononuclear cells. In the cortex were numerous minute cicatrices often infiltrated with lymphoid and plasma cells.

The glomerular lesions of the kidneys were interpreted as due to the streptococcus infection and principally of embolic or thrombotic origin, and as representing the renal participation of processes seen in the lungs,

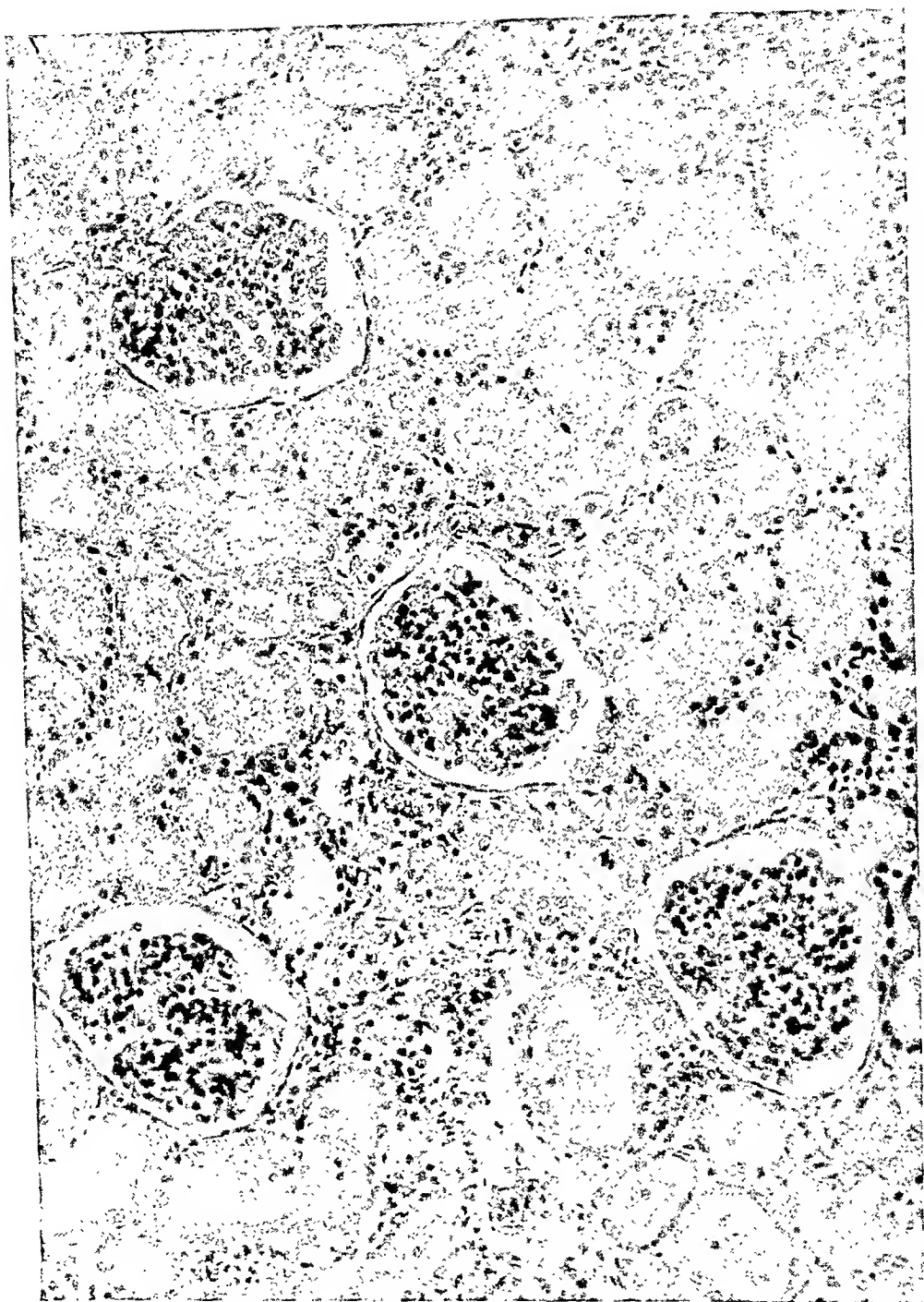


FIG. 1.—Kidney, Case V. Albuminuria and edema for three months. Note the normal appearance of glomeruli and evidences of moderate degeneration of tubular epithelium.

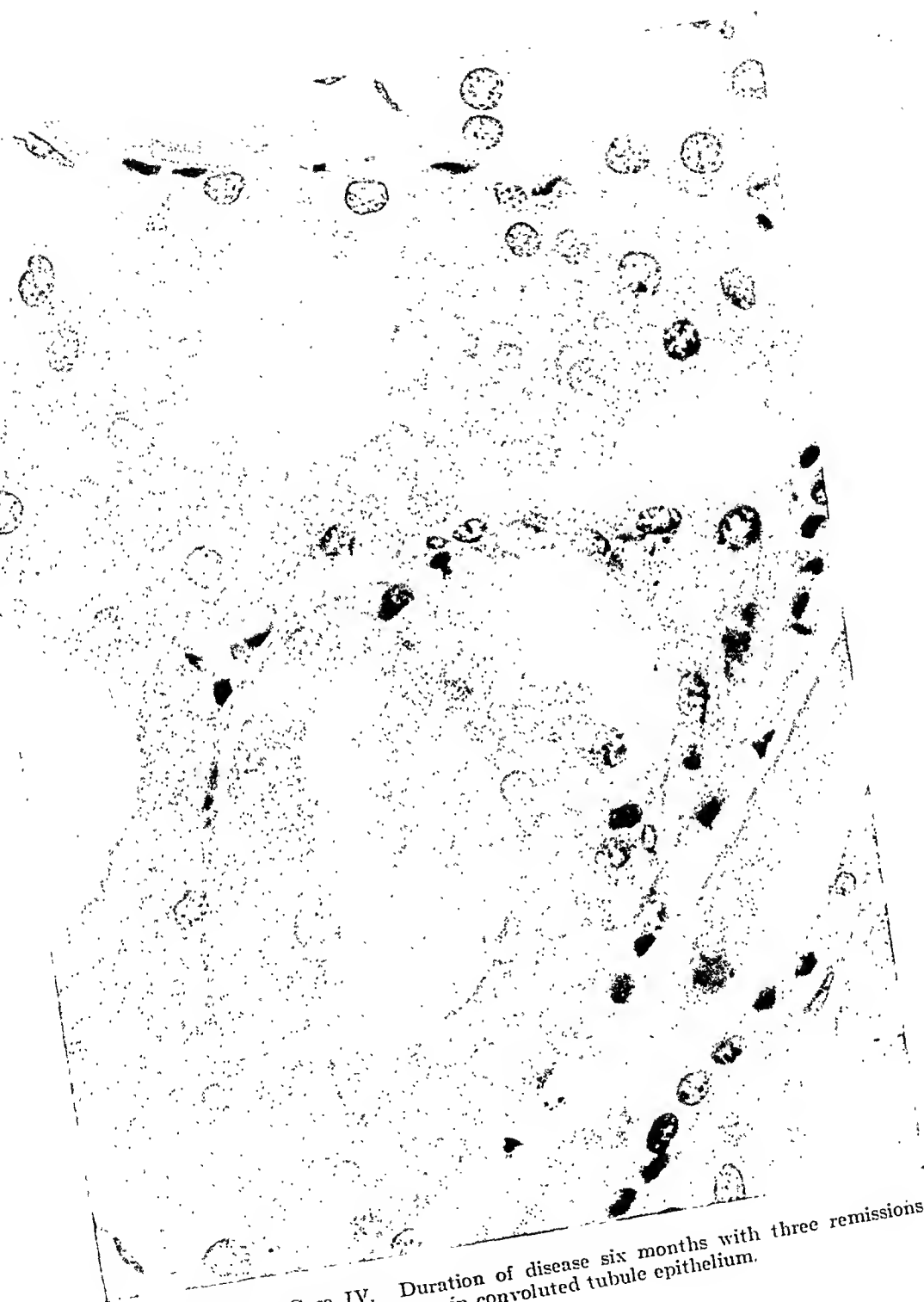


FIG. 2.—Kidney, Case IV. Duration of disease six months with three remissions. Colloid droplets in convoluted tubule epithelium.

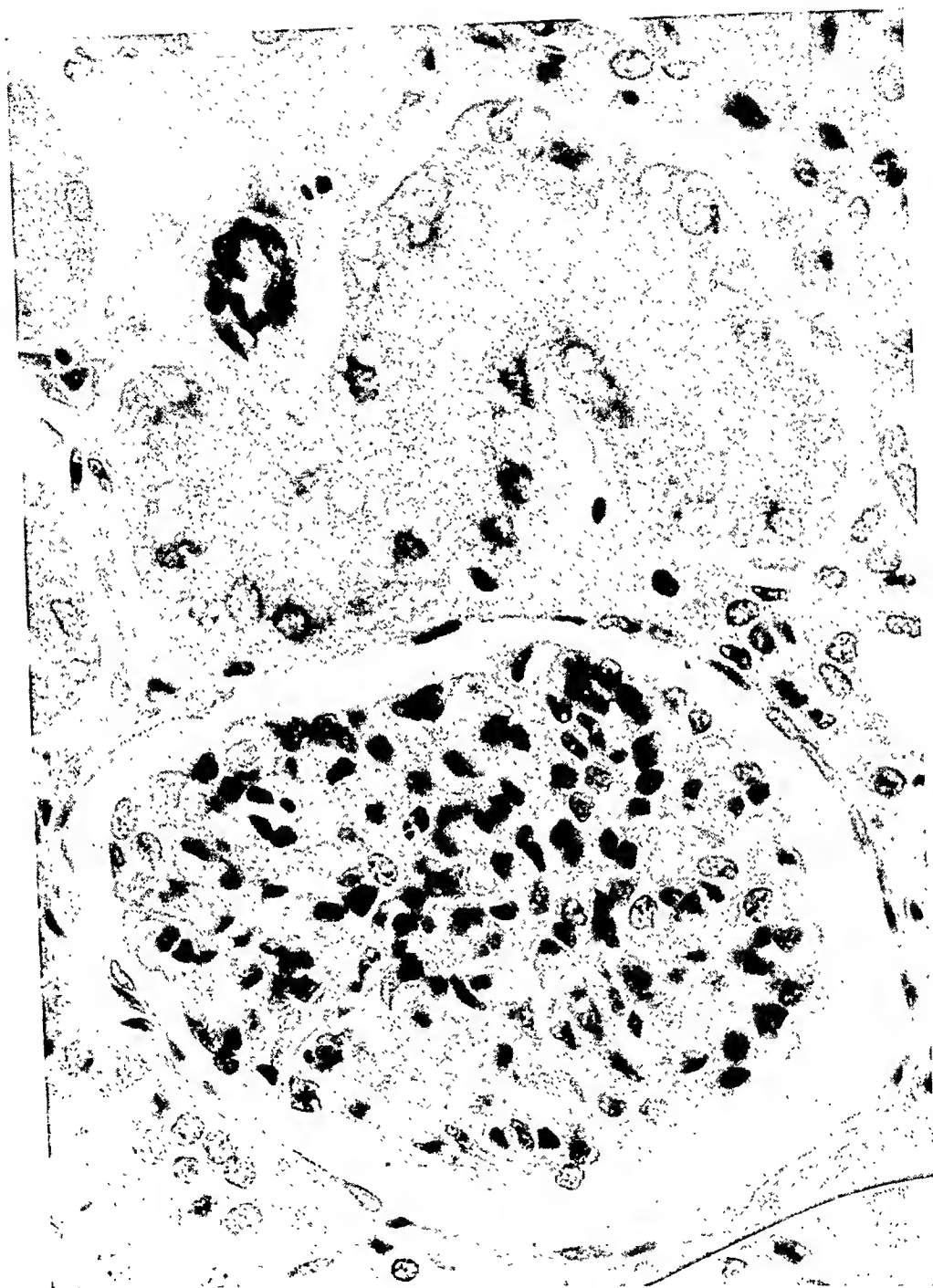


FIG. 3.—Kidney, Case III. Duration of disease four months with two remissions. Note normal glomerulus. To show marked fat vacuolization of epithelium of convoluted tubules.




FIG. 4.—Kidney, Case III. Another field showing complete necrosis of a convoluted tubule and consequent reaction in the interstitial tissue.

This is a black and white photomicrograph of a kidney section. The image shows a large area of tissue with numerous dark, irregularly shaped spots and patches, which are indicative of necrosis and an inflammatory reaction in the interstitial tissue. The overall texture is grainy and high-contrast, typical of older medical photography. The caption at the bottom identifies this as Case III, showing the complete necrosis of a convoluted tubule and the subsequent reaction in the surrounding interstitial tissue.

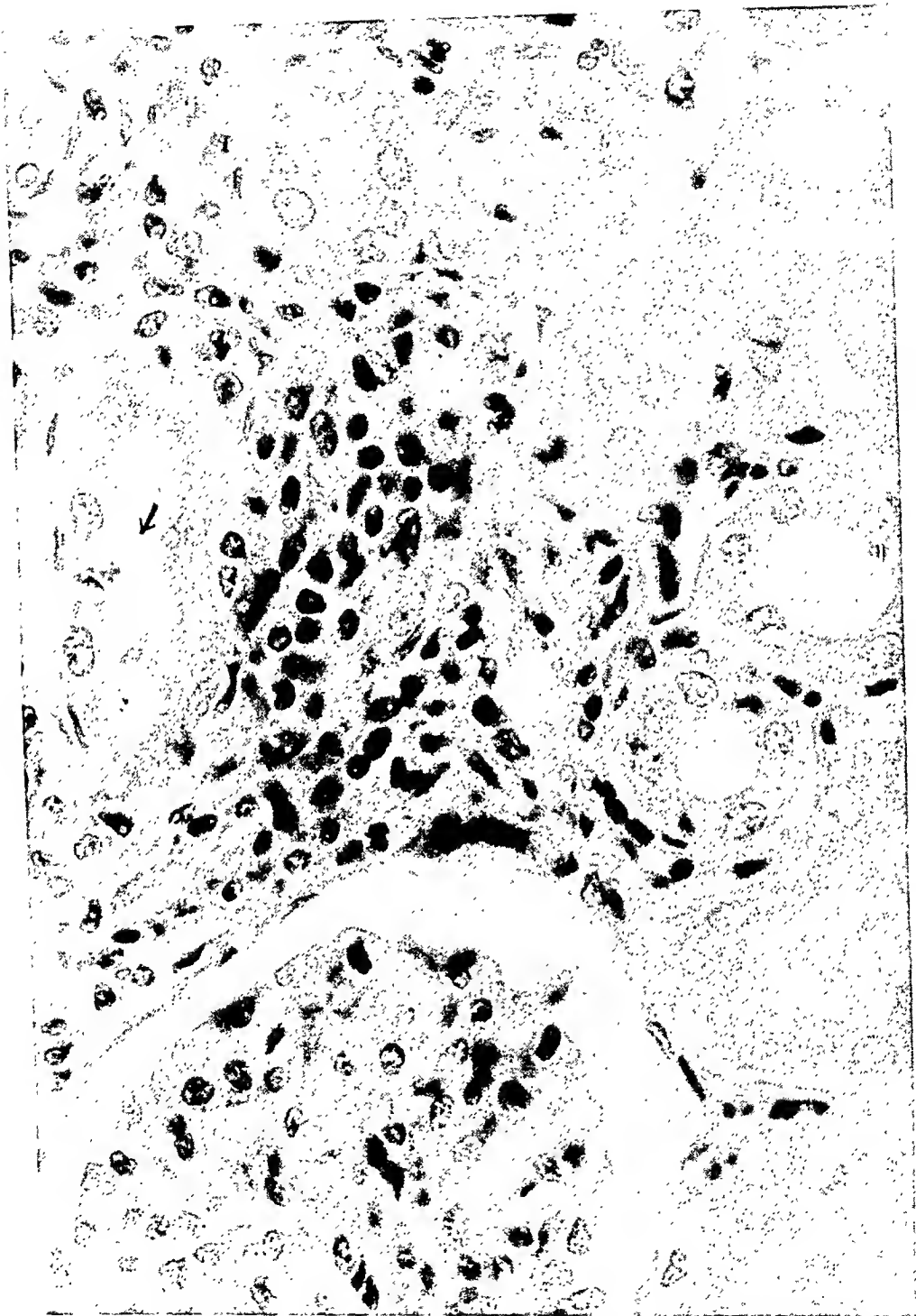


FIG. 5.—Kidney, Case III. Another field to show an early cicatrix resulting from the complete necrosis of a convoluted tubule. Above is a convoluted epithelial cell in mitosis.

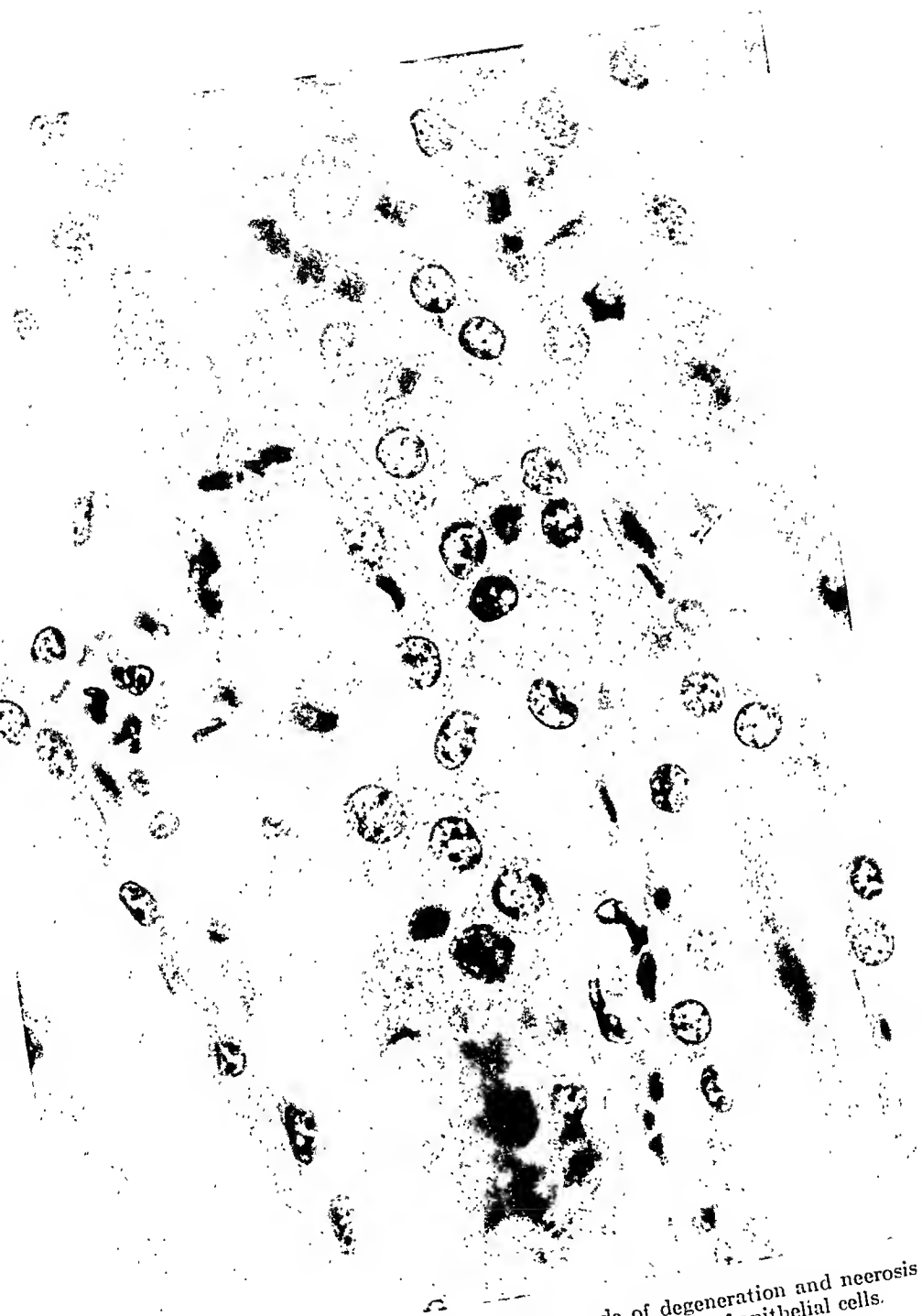


FIG. 6.—Kidney, Case VII. To show a severe grade of degeneration and necrosis of convoluted tubules and regeneration by mitotic division of epithelial cells.



FIG. 7.—Kidney, Case VII. To show normal glomerulus and mitoses in convoluted tubules.

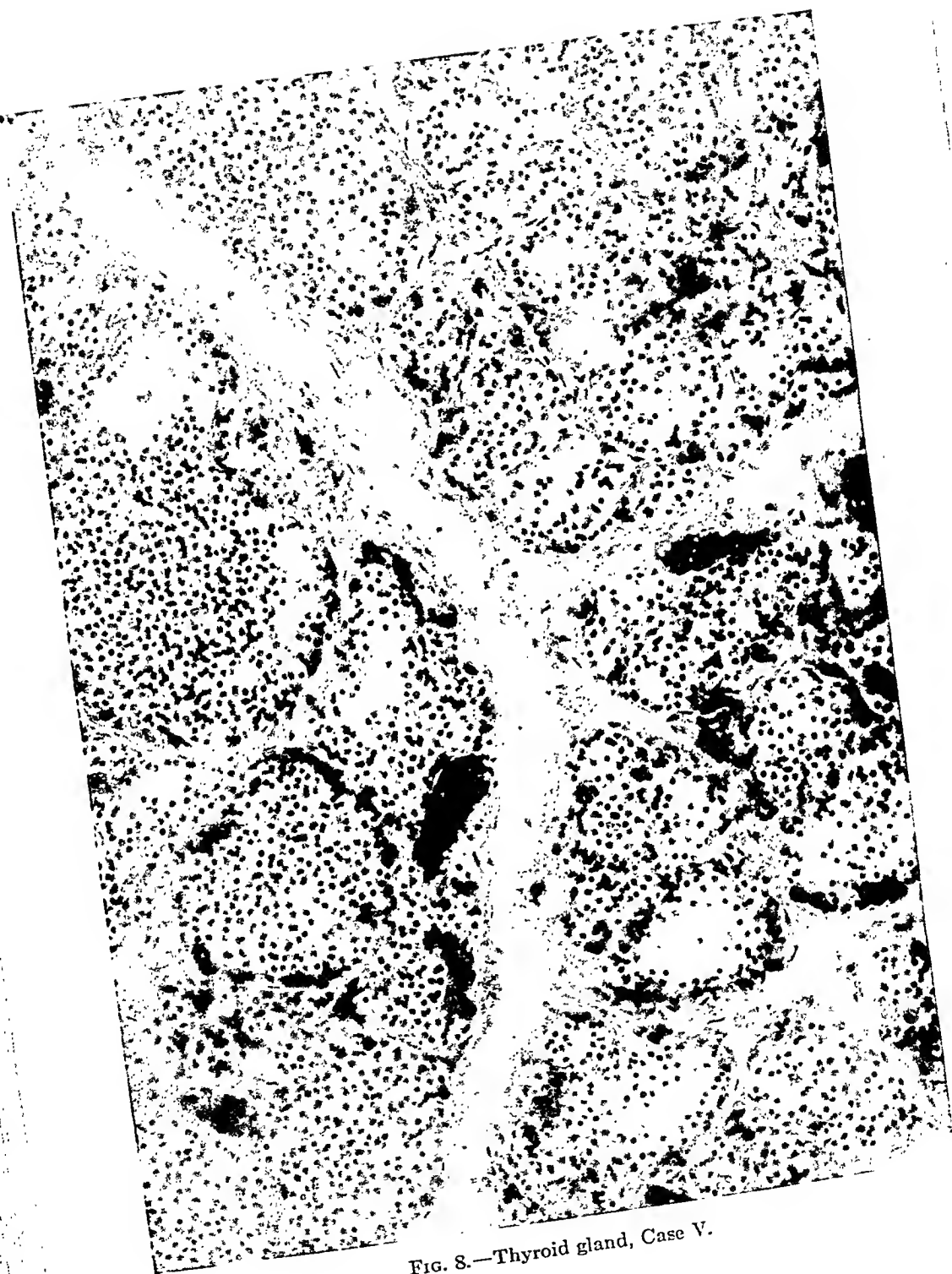


FIG. 8.—Thyroid gland, Case V.



FIG. 9.—Thyroid gland, Case VIII.

spleen and liver. The cicatrices were interpreted as due to repair following necrosis of tubules. The outstanding lesion was the acute severe tubular degeneration.

CASE V.—L. L., aged two years (Hospital No. 80943) was taken ill with coryza, rhinitis and fever and one week later edema of the eyelids developed. He did not appear seriously ill, and played about the house as usual, but as albumin was found in the urine, the patient was brought to the hospital.

Examination revealed generalized edema with a considerable amount of free fluid in the abdominal cavity. The outstanding feature in this case was the extreme edema which, in spite of treatment, varied considerably in degree and in distribution. On one occasion the eyes were completely closed and a few days later the edema disappeared from the face and the scrotum and penis became edematous. During the course in the hospital, various therapeutic measures were instituted: (1) Sodium bicarbonate; (2) calcium chlorid; (3) urea; (4) transfusion; (5) abdominal paracentesis; (6) low-protein salt-free diet; (7) high-protein diet; (8) the antra were opened and drained. These measures were ineffective and three months after admission many petechial lesions appeared, the respiration became rapid and labored and death ensued two hours after a generalized convulsion. During this period of illness the blood pressure was not raised and there were no evidences of increased cerebral pressure. The urinary output was apparently not diminished.

Laboratory Data. *Urine:* Specific gravity, 1030; 7 gm. of albumin per liter; a few hyalin and granular casts; a few leukocytes; no red blood cells. *Plasma protein,* 5.34 per cent. Antra, cultures staphylococcus albus. *Blood pressure,* 104/50, 95/65, 100/70.

Summary (by Dr. Blackfan before the autopsy). The onset with rhinitis, coryza and fever, evidently from an acute infection is not commonly found in acute tubular nephritis. Nevertheless, the clinical course and laboratory data were consistent with the disease. On these grounds it would seem probable that the histologic changes would be in the uriniferous tubules.

Autopsy (A-25-90) (nineteen and a half hours postmortem). There was marked generalized edema. The peritoneal cavity contained about 3 liters of cloudy liquid with flakes of fibrin; each pleural cavity contained 1½ liters of similar fibrin-speckled liquid. The pericardial cavity contained 500 cc. of turbid liquid. Peritoneal and pleural surfaces were injected and fibrin covered, smears from the peritoneal exudate contained Gram-positive diplococci and Gram-negative bacilli. The immediate cause of death was presumably acute peritonitis and pleuritis.

The heart weighed 50 gm. and was essentially normal.

Lungs. The left weighed 80 gm., the right 108 gm. The picture was that of fibrinous pleurisy, congestion and edema, with acute alveolar emphysema. The bronchi were free from exudate.

Spleen. The spleen weighed 40 gm. and showed the expected changes of acute peritonitis.

The pancreas showed marked edema of the connective-tissue structures.

The gastrointestinal tract showed no lesions in gross.

The liver weighed 780 gm. It was very firm (in contrast to other tissues), smooth, finely-mottled deep red and yellow. On section it yielded much blood, and its firmness was probably due to engorgement. Microscopically, extreme engorgement was the outstanding feature. There were a few minute necroses, especially about the central (hepatic) veins and rarely a small fibrin thrombus in a sinusoid. The liver cells in general were small, granular and free from vacuolization. They were reduced in size, often rounded in shape, occasionally stained deep red with pyknotic nuclei.

The adrenal glands showed considerable lipoid vacuolization.

The *thyroid gland* and organs of the neck were apparently normal. Microscopically, the thyroid proved to be remarkable for its extraordinary injection of the capillaries, complete absence of colloid and the small size and desquamation of the epithelial cells. A few follicles contained lightly staining colloid. The epithelial cells were small with prominent normal-appearing nuclei, no mitoses. There was marked edema of all the connective-tissue structure.

The *brain* weighed 1100 gm. It was very soft, and there was evidence of marked edema throughout. Microscopically, no cellular reaction was found. The *Kidneys*. The left weighed 110 gm., the right 108 gm. They were enlarged, yellowish in color, mottled with red, soft and succulent. On section the cortex and interpyramidal regions seemed swollen, the medullary rays were unusually conspicuous because of the opaque-yellowish color with deeply congested bloodvessels. The cortex was flecked with minute opaque-yellowish areas. The pelvis and ureters were normal. Microscopically, the outstanding feature was the severe and extensive degeneration of the epithelium of the convoluted and ascending Henle's tubules. The tubules were dilated, filled with granular debris and circular reticulum and granular and hyalin casts. The epithelium was swollen and finely granular or narrowed to a mere fringe. Swollen cells appeared to be discharging their cytoplasm in bud and stream-like processes into the lumina. Very few tubules, however, contained necrotic cells, and these only in isolated instances. No complete destruction of tubules was found. There was a marked basal fat vacuolization of the epithelial cells in many proximal and distal convoluted and ascending Henle tubules. Numerous ones, however, showed some blocking of capillaries by polymorphonuclear leukocytes and swollen endothelial cells, not greater, however, than that which accompanies many infectious diseases. There were no cicatrices and the picture was that of recent injury with no possibility of estimating the duration of the injury to the tubular epithelium.

The middle ears were normal. The antra of Highmore contained a thin reddish liquid. Cultures from the right yield *staphylococcus*, from the left a Gram-negative bacillus.

CASE VI.—W. L., aged two years (Hospital No. 92574). Following an illness of two days with fever, vomiting, coryza and cough, edema of the legs was noticed. The patient played around the house, apparently as well as usual, until a week later, when the abdomen became noticeably enlarged and generalized edema developed. He was brought to the hospital because of the edema which had been present for one month. The parents were quite certain that the urine had not been bloody. *Examination* revealed generalized edema with free fluid in pleural and peritoneal cavities. No primary focus of infection was found. He did not appear acutely ill on admission. On the eighth day after admission, the temperature rose gradually, he became worse and died four days later with evidences of pneumonia, empyema, peritonitis and meningitis. The blood culture showed pneumococcus.

Laboratory Data. Urine: Specific gravity, 1025; trace of albumin; few hyalin and granular casts; a few leukocytes; on the first day erythrocytes were found by none thereafter. Blood: White blood cells, 163,000; 74 per cent polymorphonuclears. Plasma protein, 4.18; N.P.N., 26.7. Blood culture and peritoneal fluid, pneumococcus.

Summary (by Dr. Blackfan before the autopsy). The onset with signs of an acute infection was followed in two days by edema of the legs. One week later generalized edema and ascites developed. The patient died five weeks after the onset with a widespread terminal infection. The onset and clinical course even are not typical of acute tubular nephritis. On the

other hand, the generalized edema, and terminal infection and the laboratory data, except for the presence of a few red blood cells during the first few days in the hospital are consistent with acute tubular nephritis (N.P.N., 26.7 mg.; plasma protein, 4.18 per cent; blood pressure, 90 mm.). It would be most surprising if the histologic examination showed degenerative changes in the tubules without as well, changes in the other parts of the renal units.

Autopsy (A-26-57) (two hours postmortem). The immediate cause of death was acute fibrinopurulent peritonitis, pleuritis (bilateral) due to the pneumococcus. There was generalized edema. The peritoneal cavity contained about 200 cc. of turbid fibrin-flecked liquid. Each pleural cavity contained about 200 cc. of similar liquid.

The *heart* weighed 42 gm. There was slight edema of the interstitial tissue.

Lungs. The left weighed 67 gm.; the right 95 gm. The pleural surfaces were in part covered with a nonadherent fibrinous exudate. The lungs in gross and microscopically showed evidence only of moderate atelectasis in portions. The bronchi and alveoli were free from exudate.

Spleen. Weight, 34 gm. It showed no relevant changes.

Pancreas. Normal.

The Gastrointestinal Tract. Normal.

The *liver* weighed 400 gm. Its surface was covered with fibrinous exudate. Its gross appearance was not remarkable. Microscopically, the parenchyma was essentially negative though the liver cells in central halves of the lobules were reduced in size and occasionally round in shape with discontinuity. Occasional cells lining sinusoids were swollen and vacuolated; there was much granular debris between liver columns and sinusoids, probably an indication of edema.

Adrenals. Microscopically, there was marked engorgement with blood, but cortex and medulla were normal.

The Brain. It was soft and microscopically the cortex showed moderate vacuolization and dilatation of perivascular spaces probably due to edema. The meninges were injected but were free from exudate.

The Kidneys. The left weighed 44 gm., the right 48 gm. They were light brown in color, and slightly soft, but not remarkable in appearance. Pelvis and ureters were normal.

Microscopically, the prominent feature was the uniform and marked changes in the tubules, though these were less striking (severe) than in any of the preceding cases. The epithelium of all tubules was affected. That of the convoluted and ascending Henle tubules was unusually swollen and finely granular with only rare cells showing pyknotic nuclei. Very rarely an isolated cell of these tubules was densely stained with eosin and shrunken, the nucleus pyknotic. None of the tubules showed extensive necrosis. All contained granular debris and circular reticulum and some contain hyalin casts, which were numerous in the collecting tubules. The descending tubules of Henle were dilated, filled with granular debris and the cells were reduced to flat platelike objects, the nuclei appeared normal. In the upper portions of these tubules the cytoplasm was more nearly normal in amount and frequently contained coarse, brown, granular pigment. The proximal convoluted tubules contained a moderate amount of fat in small globules which stained deeply with Scharlach R. Numerous glomeruli showed minute droplets in the endothelium. This fat was isotrophic.

The *glomeruli* were with rare exceptions completely normal. The exceptions showed moderate swelling of the endothelium of the capillaries and hence contained less blood. Also an occasional glomerulus containing coarse strands of fibrin in the capillaries. This kidney contained no cicatrices like those of the preceding cases.

The middle ears, frontal and sphenoidal sinuses were normal.

CASE VII. — T. F., aged three years (history lost). *Laboratory data:* *Urine:* Specific gravity, 1025; marked trace of albumin; hyalin and granular casts; no erythrocytes. Phenolsulphonephthalein, 45 per cent. *Blood:* White blood cells, 25,000 per. com.; polymorphonuclears, 70 per cent; plasma protein, 4.2 per cent; N.P.N., 40 mg. per cent. *Blood pressure:* 100/60.

Summary (by Dr. Blackfan before autopsy). The insidious onset with the characteristic urinary and blood data and the terminal infection suggested that the histologic changes would be degenerative lesions in the tubules, without glomerular lesions.

Autopsy (A-25-88) (one and a half hours postmortem). The immediate cause of death was a generalized fibrinopurulent peritonitis. There was a generalized edema, much thin puriform liquid in the abdominal cavity and a few cubic centimeters of turbid, yellowish liquid in each pleural cavity.

The *heart* weighed 80 gm. The gross and microscopic appearance were normal.

Lungs. The left weighed 88 gm., the right 104 gm. Both were edematous. Microscopically, there was an early bronchitis, peribronchitis and pneumonitis.

Spleen. Weight, 90 gm. It showed no relevant changes.

Liver. Weighed 620 gm. It was somewhat enlarged. The color was mottled red and yellow in areas of lobular dimensions. Microscopically, there was very marked engorgement of the sinusoids with blood. The sinuses contained numerous mononuclear phagocytes and occasional polymorphonuclear leukocytes, and the endothelium was separated from the liver columns by empty spaces interpreted as evidence of edema. The liver cells contain small vacuoles (fat). Occasional ones are deeply stained with eosin. All seemed reduced in size.

Pancreas. Normal.

Gastrointestinal Tract. Normal except for the acute peritonitis.

The *adrenal glands* were markedly engorged. The glomerular zone showed very little lipoid vacuolization. In the fascicular zone were numerous small necroses, usually with disappearance of the adrenal cells and replacement by mononuclear phagocytes and polymorphonuclear leukocytes.

The Brain. There was slight edema.

Kidneys. The left weighed 90 gm., the right 86 gm. They were enlarged, deep red with a very fine pale mottling. The pelves and ureters were normal.

Microscopically, the outstanding feature was the severe and extensive degeneration of the convoluted and ascending Henle tubules. These tubules were universally affected, the least degree being swelling and increased granularity of the cells accompanied by a fine fat vacuolization. (This fat stained red with Scharlach R.) Very few cells contained hyalin droplets. Greater degree of injury was shown by reduction in size of the cells and the presence of densely staining acidophilic masses in the cytoplasm. A few tubules are completely necrotic, with lumina filled with globular hyaline masses. There were numerous mitotic figures in the tubules with this massive hyalin degeneration of the cells and in such instances the picture was reminiscent of that of corrosive sublimate poisoning. The most marked lesions were in the convoluted tubules, blood corpuscles filled occasional convoluted tubules, the others were filled with granular debris, circular reticulum or rarely hyalin casts. The latter were in practically every collecting tubule. The glomeruli were practically normal, a rare one contained a few polymorphonuclear leukocytes and clumps of fused red blood corpuscles. The interstitial tissue was free from wandering cells. There were no cicatrices. The condition of these kidneys may be expressed as that of severe acute tubular degeneration singularly uncomplicated by other lesions.

The middle ears and accessory respiratory sinuses of the skull were normal.

CASE VIII.—V. C., aged twenty-two months (Infants' Hospital No. 92574). With the exception of having had measles when eight months of age, had been regarded as a normal baby until she was fourteen months of age. Then there followed a series of episodes which are of interest. At fourteen months an attack of vomiting which continued for a few days. One week later, the eyelids were swollen. When sixteen months of age puffiness of the eyelids was again observed. Each time the edema lasted only a few days. From then until twenty-one months of age she continued in good health. Three weeks before admission the eyelids again became swollen, this was followed by enlargement of the abdomen. Albumin in large amounts was found in the urine. No blood or red cells were present.

Examination showed generalized soft, pitting edema with free fluid in the peritoneal cavity. No focus of infection was found. She appeared acutely ill. Edema rapidly increased as shown by a gain of 3 pounds in six days.

The patient became extremely drowsy and after four days of fever (105° F.) died.

Laboratory Data. *Urine:* Specific gravity, 1025; marked trace of albumin; many hyalin casts; no erythrocytes.

Blood. White blood cells, 19,000 per c.cm.; polymorphonuclears, 54 per cent; plasma protein, 3.2 per cent; N.P.N., 44 mg. per cent.

Blood Cultures. Pneumococcus (700 colonies per cubic centimeter).

Blood pressure steadily increased in six days from 120/100 to 170/105 mm. just before death.

Summary (by Dr. Blackfan before the autopsy). It is possible that the edema of the eyelids which occurred first when the child was fourteen months of age, indicated the onset of the disease; that it recurred when she was sixteen months of age and again when she was twenty-one months of age with a terminal pneumococcus septicemia one month later. The clinical course, physical findings and termination are characteristic of acute tubular nephritis as was the plasma protein and the urinary findings. The one outstanding feature which was difficult of explanation in this type of nephritis was the blood pressure. We have never seen hypertension of this degree (170 mm.) in this form of nephritis and so reasoned that this was of the mixed type (glomerulotubular nephritis).

Autopsy (A-29-19) (thirteen and a half hours postmortem). The immediate cause of death was a fibropurulent peritonitis which followed a pneumococcus septicemia. There was generalized edema. The peritoneal cavity contained approximately 500 cc. of pale milky liquid with much pale yellowish fibrin; smears showed Gram-negative bacilli and Gram-positive diplococci identified respectively as the Colon bacillus and Streptococcus viridans. Each pleural cavity contained approximately 200 cc. of exudate similar to that in the abdominal cavity.

The heart weighed 62 gm. and was normal.

Lungs. The left weighed 94 gm., the right 118 gm. The pleural surfaces of both were injected and covered with a thin layer of fibrin. They were both congested, with some alveolar collapse.

Spleen. Weighed 50 gm. It showed no relevant changes.

Pancreas. There was marked edema and diffuse infiltration with moderate numbers of lymphoid cells.

The Gastrointestinal Tract. Normal.

Liver. Weighed 600 gm. The gross appearance was not remarkable, though somewhat paler than normal. Microscopically, there was no evidence of the usual type of fat vacuolization. The central halves of most

lobules showed lighter-stained liver cells reduced in size and often rounded in shape with a peculiar mottling. These cells with high power proved to be very finely vacuolated; the mottling was due to deeply basic-stained (hematoxylin) bodies arranged peripherally in the cells. These bodies are of irregular shapes though often circular or ovoid and 1 to 3 microns in diameter. They probably represent an early effect of cell degeneration. There were a few minute focal necroses scattered throughout the sections without reference to anatomical structures.

Adrenal Glands. Were congested with markedly diminished lipid.

The *thymus* was small. Microscopically, it showed marked atrophy.

Thyroid gland was apparently normal in gross. Microscopically, it presented the same extraordinary appearances of the thyroid gland of Case V. There was complete absence of normal colloid. Most of the alveoli were collapsed, contained many desquamated clearly stained thyroid cells and a small amount of granular material. The capillaries are enormously engorged, tortuous and projected deeply into the alveoli where these were not collapsed; by their prominence they obscured the architecture of the gland. The thyroid epithelium was atrophic, the cytoplasm scanty, finely granular with uncertain outlines. Many nuclei were pyknotic.

Brain. Weighed 1168 gm. There was moderate edema. Microscopically, no cellular lesions were found. There was marked vacuolization of the cortex and basal nuclei and great dilatation of perivascular spaces in the cortex, basal ganglia and fiber tracts which were interpreted as evidences of edema.

Kidneys. The left weighed 73 gm., the right 65 gm. They were smooth, everted slightly from the capsules when incised. The cortices were pale, uniformly yellowish in color. The pyramids, pelvis and ureters were normal.

Microscopically, the glomeruli were normal, all showed patent capillaries with a moderate injection with blood. The capsular spaces containing small amounts of fine granular precipitate. The prominent feature was the uniform change in the tubules comparable in severity to Case VI. The convoluted tubules were dilated and filled with granular precipitate and circular reticulum. The epithelial cells were granular, swollen in some instances, in others reduced in size with shaggy free borders. The nuclei stained normally and there was no evidence of actual necrosis of cell. The ascending tubules of Henle's loops showed similar granular degenerative change. Casts were very rare; a few of the hyalin type were found in Henle tubules. Scharlach R stains showed a surprisingly large amount of fat, very uniformly distributed in the convoluted tubules. The droplets were of small size basally situated, and only a rare anisotropic droplet could be found by examination with polarized light.

This kidney contained no cicatrices. No necrosis of tubular epithelium could be found and the histologic appearances were those of a mild process comparable to the type of renal lesions found incidentally so frequently in the routine study of tissues from individuals who died of infectious diseases.

Discussion. *The Kidney.* The kidneys of these 8 children without much possibility for doubt all exhibited the effects of the same disease, characterized by degenerative changes in the epithelium of the convoluted tubules. The mildest recognizable injury was comparable to that usually called cloudy swelling and evidenced by increased affinity for acid dyes and swollen and granular cytoplasm (Fig. 1) (Fahr's first stage), a condition which we have seen produced by prolonged experimental acidosis. (See Seegal below.)

Severer grades were indicated by the presence of hyalin or colloid droplets in the cells (Fig. 2) (Fahr's second stage) or even complete necrosis of all the cells in segments or the whole of tubules (Fahr's third stage). In the severest lesions the presence in the cells of densely stained hyalin material recalled the effect of corrosive sublimate poisoning (Figs. 4 and 6).

The kidneys of Cases I, II, III and IV contained small cicatrices which were without legitimate question the late or end result of complete necrosis of tubules and consequent elimination of glomeruli. In Case III the kidneys (Figs. 3, 4 and 5) showed all stages in sequence from necrosis through cellular infiltration to fibrosis. Also, the distribution and small size of these scars could only be explained by this interpretation. The presence of cicatrices in each instance conformed to a history of at least two remissions in the signs and symptoms of renal disease.

The lesions of the tubular epithelium found at death in each instance may be regarded as the effects of the disease covering the period of illness before death, that is, the last exacerbation or in Cases V, VI and VII of the entire comparatively brief duration of the disease. In every instance, however, we are warranted in believing that the tubular lesions represented the effects of an attack or exacerbation lasting from a few weeks to several months. In no instance was there cellular infiltration of the interstitial tissue of the kidneys except immediately adjacent to necrotic tubular epithelium.

From the above facts one important conclusion may be made: That whatever degree of injury may have existed in the kidney at any one period, the effect is not cumulative. With the exception of complete necrosis of large portions of tubules repair is probably completely accomplished during remissions, while there is histologic proof of replacement of individual necrotic cells by mitotic division of adjacent cells during exacerbations (Figs. 5, 6 and 7). Whether the tubular degeneration of this disease can end in a notably scarred or "contracted" kidney is open to question. Theoretically, on the basis of the cicatrices which we have found and explained as the result of repair following necrosis of tubules, a contracted and insufficient kidney should be a possible outcome.

We must, however, consider whether the lesions found at death were due to terminal events or whether the tubular epithelium throughout each exacerbation was injured to a degree morphologically demonstrable. This is a difficult and perhaps impossible question to answer without biopsy material. The continuous albuminuria and presence of cells and casts in the urine during the attacks or exacerbations support the belief that the tubules are the seat of demonstrable injury. The explanation of the histogenesis of some urinary casts advanced by Jackson² necessitates a degree of injury comparable to those we have found at autopsies in the milder degrees

of injury in this series of 8 cases. Incidentally, our histologic studies of this series corroborate the findings of Jackson in regard to the direct derivation from renal epithelium of the material from which certain types of casts are formed.

There is also experimental evidence for the long continuance of injury of the tubular epithelium in the work of Seegal,³ who showed that in long maintained acidosis in rabbits and dogs produced by the continued administration of tenth-normal hydrochloric acid or of ammonium chlorid (periods up to one year) casts and albumin appeared in the urine throughout the experimental period. She found in the kidneys removed surgically or upon sacrifice of the animals acute degeneration of the epithelium of the convoluted tubules with pyknosis of occasional nuclei and regeneration in cases of longest duration. While the continuous presence of damaged though viable epithelium seems to be the more probable state of affairs in the kidneys of this type of nephritis, routine experiences in the correlation of clinical histories and postmortem material prove the frequent production of similar tubular lesions of even greater severity in a very few days in numerous types of severe infections and toxic diseases in children. Hence the histology of the kidneys gives no clue to the duration of the disease in tubular nephritis unless there are present the cicatrices of lesions of earlier date. The facts force us to seriously consider the possibility of a long-sustained (chronic?) lesion of cells morphologically in a state of acute injury.

The infections which terminate this disease must modify the pathologic histology in the direction of severity. In Case IV the terminal streptococcus infection accompanied by multiple thromboses in lungs and spleen was undoubtedly responsible for the glomerular thromboses. In other cases of the series the slight glomerular lesions could be accounted for as secondary to severe tubular degeneration. In Cases VI and VII, the only ones in which pneumococcus infections were prominent, the renal lesions were least severe.

In but 2 cases, Case III (Fig. 3) and Case VIII, was the quantity of fat a conspicuous feature in the tubular epithelium. In no instance was the fat doubly refractive, though in casts *in situ* in the kidney of Case III fatty acid crystals and doubly refractive lipoid globules were found. The failure to find doubly refractive lipoid in the kidneys from individuals who showed it in the urine during life agrees with the 2 cases studied postmortem which Eckstein⁴ reported. The case terminated with pneumococcus peritonitis and glomerulonephritis; the other was a case of tuberculosis with amyloidosis. Doubly refractive lipoids were present in the urines of both. None could be demonstrated in the kidneys after death.

The Thyroid. The thyroid glands of Cases V and VIII (Figs. 8 and 9) are of interest. The changes described, absence of colloid,

atrophy and desquamation of epithelial cells and extreme vascular engorgement may be interpreted as exhaustion effects following excessive functional performance. They demand further study when opportunity offers.

Depletion of colloid and epithelial desquamation occurs in many infectious diseases, and, according to Wegelin,⁴ particularly in scarlet fever, smallpox and diphtheria, but also in measles, typhus, pneumonia, epidemic and tuberculous meningitis, tetanus, acute peritonitis and progressive wound infections. Most of these conditions are frequently accompanied by degeneration of the convoluted tubules of the kidneys, yet our own studies show that even in some of the above where severe tubular lesions have been found the thyroid has been normal. In our Warsaw series of typhus autopsies no notable instance of colloid depletion was found in the thyroid. A review of the material shows a slight change in a small number of cases.

In infants and children a review of 77 postmortems revealed 7 instances of notable colloid depletion so that the thyroid appearances recalled or approximated those of Cases V and VII. Two of these were in children who died of milk-borne *streptococcus epidemicus* septicemia; both showed streptococci and thrombi in the glomeruli as well as marked tubular degeneration in the kidneys. Three instances were in infants who died of acute nutritional disturbance with persistent vomiting and dehydration; 1 showed normal kidneys, 1 cloudy swelling of the convoluted tubules and 1 with a severe grade of degeneration of the tubular epithelium. One case was that of an infant, aged thirteen months, with acrodynia, terminating with thrush, bronchitis, peribronchitis and pneumonia. The kidneys showed glomerulonephritis and severe tubular degeneration. One case was that of a boy, aged seven years, who died of fat embolism following an operation for fixation of a tuberculous hip. The kidneys showed cloudy swelling only. In no instance, however, was the thyroid completely depleted of colloid nor were the engorgement and desquamation pronounced.

Eight cases of glomerulonephritis, 2 of long duration, 1 terminating with pneumonia and empyema show normal thyroids with no trace of colloid depletion, engorgement or epithelial desquamation. It would occupy too much space to review the histories and postmortems of the cases with severe infectious processes where the thyroid was normal and kidneys showed tubular degeneration. Our opinions are: (1) That thyroid depletion of the character described occurs independently of the nature of the infecting microorganism; (2) that it is always associated with degeneration of the convoluted tubules; (3) that it may not be found though both infections and tubular degeneration are found; (4) that in typical glomerular nephritis with edema, albuminuria and severe secondary tubular lesions it is characteristically absent; and (5) that it is prob-

ably dependent upon grave metabolic disturbance, presumably often the result of infections of unknown etiology as in the acute nutritional disturbances of infants and in so-called nephrosis. Another approach to the consideration of the thyroid change is suggested by the reports of tubular degeneration accompanied by fat in the epithelial cells and sometimes by cellular infiltration of interstitial tissue and tubules in the kidneys after extirpation of the thyroid gland in carnivora. Wegelin⁵ gives a brief review of the subject. We have consulted the original articles upon which he based his review with the exception of one inaccessible at present, that of Rosenblatt.⁷

Blum⁸ used dogs, and after thyroid extirpation found regularly degeneration of the epithelium of the convoluted tubules and in long survivals infiltration of the interstitial tissues with round cells, thickening of glomerular capsule and frequently hemorrhages into the parenchyma. He also described toxic fatty degeneration of the liver cells.

Bensen⁹ and Kishi¹⁰ used cats and dogs for their experiments and reported substantially the same results as Blum, including the fatty degeneration of renal tubules. Hagenbach¹¹ mentions only very briefly the fatty degeneration of the convoluted tubules in cats after thyroid extirpation. He also found degeneration of liver cells as described by Blum.

The Liver. The livers of these cases are worthy of special consideration. Unfortunately, owing to restrictions, no weights were obtained in 2 and no histologic material in 1. Four of the series showed marked increase in weight, in 2 instances almost double normal, and in 2 the weight was normal for the age. Where the weight was increased, histologic examination shows that it was due to extraordinary and uniform engorgement of the sinusoids. Without exception the parenchyma cells of these livers were reduced in size; in most instances this was quite marked in the central halves of the lobules, while in other instances many of the liver cells were rounded in outline, giving the effect of discontinuity of columns. Other changes common to the series were those interpreted as due to minor degrees of cellular injury, increased acidophilic stain, fine vacuolization and the presence of a peculiar basic staining reticulum. All of the livers showed considerable granular debris between the liver columns and sinusoids which, together with peripheral vacuolization cells in many instances seemed to warrant the diagnosis of edema. In 2 of the livers there were striking effects unquestionably due to the terminal infections, inasmuch as there were numerous minute thrombi in the sinusoids. In view of the recent work by Thomas, Schlegel and Andrews,¹² by Welker, Andrews and Thomas,¹³ and by Andrews, Thomas and Welker,¹⁴ the histologic changes in our series deserves more than casual attention. These workers in the experimental production of uremia by

injections of hypertonic salt solution noticed profound pathologic changes in the liver cells, and were able by immunologic methods to demonstrate the presence of liver protein in the urine. We have already mentioned the association of liver-cell lesions with tubular lesions in the kidney following experimental extirpation of the thyroid gland in cats and dogs.

The same type of discussion that we have applied to the kidney lesions apply, of course, to the liver, and one may well ask what would a biopsy of the liver have shown during life in any one of these cases, for here again routine correlation of clinical histories and postmortem studies gives every reason to believe that any of the changes we have found in the liver may be produced in a very few days as a consequence of infections of one sort or another.

Conclusion. We believe that the 8 cases here presented, because of the clinical and pathologic features common to them all, are representative of a disease entity in childhood. This belief implies a common etiology or pathogenesis for the series.

The pathology of the kidneys affords no premises for the explanation of the important physiologic disturbances of the disease and, therefore, we do not believe that the primary effect of the etiologic agent is upon the kidneys or that the important manifestations of the disease are consequences of injury specific to the kidneys.

The histologically demonstrable damage to the kidneys was found in the tubules. The glomeruli showed only lesions accountable for either by the terminal infection or severe degeneration of the tubules of the same units. In general the glomeruli were without lesions.

Conclusion regarding the rôle of the thyroid in this disease is not possible. The thyroid lesion is probably a manifestation of functional exhaustion and, therefore, probably is neither cause nor direct consequence of the kidney damage.

The pathology of the liver, slight atrophy and degeneration of the hepatic cells, may also be interpreted as effects of overtaxed functional activity consequent to the loss of blood proteins.

While offering no substitute we believe that any name implying a renal origin such as nephrosis or tubular nephritis is not appropriate to this disease.

REFERENCES.

1. Davison and Salinger: Tubular Nephritis (Nephrosis) in Children and its Relationship to other forms of Nephritis, Johns Hopkins Hosp. Bull., 1927, 41, 329.
2. Jackson: The Histogenesis of Urinary Casts, Am. J. Pathol., 1927, 3, 285.
3. Seegal: Chronic Acidosis in Rabbits and in Dogs with Relation to Kidney Pathologic Change, Arch. Int. Med., 1927, 39, 550.
4. Eckstein: Zur Klinik der "Lipoidnephrose" in Kindesalter, Klin. Wehnsehr., 1926, 5, 1787.
5. Henke and Lubarsch: Handb. d. Spez. Path. Anat. u. Histol., 1926, 8, 109.
6. Henke and Lubarsch: Handb. d. Spez. Path. Anat. u. Histol., 1926, 8, 364.
7. Rosenblatt: Sur les causes de la mort des animaux thyroïdectomisés, Arch. des Sci. Biol. de St. Petersburg, 1894, vol. 3. Quoted by Weglin, Henke and Lubarsch, Handb. d. Spez. Path. Anat. u. Histol. 1926, 8, 365.

8. Blum: Ueber Nieren Veränderungen bei Ausfall der Schilddrüsen-Thätigkeit (Nephritis interstitialis auto-intoxicatoria), Virchow's Arch., 1901, 166, 403.
9. Bensen: Beitrag für Kenntniss der Organveränderungen nach Schilddrüsen extirpation, Virchow's Arch., 1902, 170, 229.
10. Kishi: Beiträge für Physiologie der Schilddrüse, Virchow's Arch., 1904, 176, 260.
11. Hagenbach: Experimentelle Studie über die Funktion der Schilddrüse und der Epithelkörperchen, Mitteil. aus den Grenzg. d. Med. u. Chir., 1908, vol. 18.
12. Thomas, Schlegel and Andrews: Urinary Proteins Not Originating in Blood, Arch. Int. Med., 1928, 41, 445.
13. Welker, Andrews and Thomas: Identity of Urinary Proteins of Nephritis, J. Am. Med. Assn., 1928, 91, 1514.
14. Andrews, Thomas and Welker: Albuminuria in the Mechanism of Detoxification, Arch. Int. Med., 1929, 43, 139.

TRANSFUSION OF BLOOD IN BRIGHT'S DISEASE.*

BY HERMAN O. MOSENTHAL,

PROFESSOR OF MEDICINE AND ATTENDING PHYSICIAN, NEW YORK POST GRADUATE
MEDICAL SCHOOL AND HOSPITAL,

AND

BENJAMIN ASHE,

ASSOCIATE IN MEDICINE AND ASSISTANT ATTENDING PHYSICIAN, NEW YORK
POST GRADUATE MEDICAL SCHOOL AND HOSPITAL.

(From the Medical Service of the New York Post Graduate Medical School and
Hospital.)

TRANSFUSIONS of blood are not resorted to very frequently in the treatment of Bright's disease. Hesitation concerning their use arises largely from impressions and is frequently not based upon an analysis of actual observations. Current objections to the use of transfusions in nephritis may be formulated as follows:

1. Blood transfusions may elevate blood pressure and change a comparatively harmless hypertension into one of alarming proportions.

2. There is a feeling among many clinicians that transfusions may, in some manner, produce toxic materials in the blood and tissues, which a damaged kidney cannot eliminate.

3. Transfusions may aggravate an existing renal lesion and thus cause progressive pathologic changes in the kidney and accentuate a renal insufficiency.

Indications for transfusions of blood in Bright's disease, which we propose to analyze, may be summarized as follows:

1. As an aid in treating the uremia attendant upon renal insufficiency.

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2. As a relief for severe anemia.

3. As a means of combating edema by raising the osmotic pressure within the circulation through an increase of the proteins of the blood.

In the past eleven years, we have had many transfusions carried out on patients suffering from Bright's disease. All of them are not reported here, but only a few are mentioned that will serve to illustrate the validity of the indications and contraindications for transfusions in Bright's disease. Some of these cases were transfused by the syringe method; the majority received blood by the direct method of Unger, and most of these transfusions were carried out by Lester and Jonas Unger whose great skill and generous efforts are appreciated by all who know their work at first hand.

The Effect of Transfusions of Blood Upon Arterial Pressure. Our experience has been that transfusions up to 1000 cc. do not increase the blood pressure, no matter how high the arterial tension may be. This is in accord with the findings of Eyster and Middleton¹ who demonstrated that in cases of pernicious anemia after transfusion equivalent to 1 to 1.5 per cent of the recipient's body weight, there was only a slight transitory rise in the systolic, diastolic and venous pressures. Table I illustrates the effect of transfusion on a hypertensive individual, moribund because of renal insufficiency brought on by a secondary contracted kidney. This case is noteworthy because the blood was given very slowly by the syringe method. No changes in the levels of blood pressure occurred as the result of the transfusion.

TABLE I.—EFFECT OF TRANSFUSION UPON BLOOD PRESSURE.

Time, P.M.	Blood pressure.		Remarks.
	Syst.	Diast.	
12.05	225	148	
12.08	220	148	100 cc. blood injected.
12.25	225	150	200 cc. blood injected.
12.36	220	143	300 cc. blood injected.
12.45	220	145	400 cc. blood injected.
			Transfusion terminated.
7.15	215	140	

January 28, 1919. H. L., male, aged twenty-one years, suffering from severe uremia brought on through renal insufficiency caused by secondary contracted kidney. The patient received 400 cc. of blood given slowly by the syringe method. There was no rise in either the systolic or diastolic pressure.

In Table II another instance of transfusion in a hypertensive individual is given. The procedure here consisted in giving 1000 cc. of blood rapidly, that is within seven minutes, by the Unger method. The blood pressure in this patient showed no increase. It is worth noting that the effect of the nervous strain incident to the preparation for transfusion did cause a very definite rise in the systolic

pressure (from 162 to 228). However, the transfusion itself did not bring about any increase of the arterial tension. It is very significant that a nervous strain can result in a rise of 66 points in systolic blood pressure while a transfusion of 1000 cc. of blood within seven minutes does not have an appreciable effect on the arterial tension. The observation, as given in Table II, shows very clearly that great care must be exercised in interpreting the cause for changes in blood pressure.

TABLE II.—THE EFFECT OF TRANSFUSION UPON BLOOD PRESSURE.

Time, P.M.	Blood pressure.		Pulse.	Remarks.
	Syst.	Diast.		
2.35	162	118	84	Lying down; preliminary to transfusion.
2.42	228	118	84	Preparing for transfusion.
2.45	204	108	90	
2.46	202	116	84	Needle inserted into vein.
2.48	228	122	84	300 cc. blood injected.
2.50	226	124	72	500 cc. blood injected.
2.51	228	122	72	700 cc. blood injected.
2.52	224	120	84	850 cc. blood injected.
2.53	220	116	78	1000 cc. blood injected; transfusion terminated.
2.57	226	124	84	Talking about transfusion.
2.59	220	122	84	
3.01	212	116	84	
3.07	220	116	84	

February 28, 1930. H. C., male, aged sixty-three years, suffering from secondary contracted kidney complicated by secondary anemia, renal insufficiency and hypertension; gout, diabetes mellitus and angina pectoris were also present. The nervous strain incident to the anticipation of the transfusion resulted in a distinct rise in blood pressure. The transfusion of 1000 cc. given rapidly by the direct method did not influence the level of the blood pressure or the pulse rate appreciably. When the apprehension concerning the transfusion was allayed, this patient's blood pressure promptly returned to its habitual level of systolic 160, diastolic 120.

A third case that may be cited, because of his very high diastolic pressure, is that of a young man, aged twenty-nine years, whose blood pressure persistently remained at a level of about 230 systolic and 160 diastolic. In addition, there was some renal insufficiency as shown by a urea N of about 50 mg. per 100 cc. of blood; there was a persistent albuminuria, and there was a secondary anemia with a hemoglobin of about 50 per cent. Because of the desperate situation of this patient, it was deemed advisable to attempt a transfusion. This was carried out and 500 cc. of blood were given by Unger's method. This did not bring about any appreciable change in the level of the blood pressure either during the transfusion or subsequently. The blood pressure was determined during the transfusion at intervals corresponding to the injection of 40 cc. of blood for each reading. A blood pressure of systolic 230, diastolic 160 at the beginning of the operation remained unchanged until 400 cc. had been

given; during the injection of the last 100 cc. the blood pressure was systolic 230, diastolic 156.

Theoretically it might be argued that transfusion of blood must raise blood pressure by increasing the blood volume. In actual practice, we have found that this is not the case. There must be compensatory factors to nullify this possible effect. Evidently the nervous control of the heart musculature, the larger bloodvessels and the arterioles is so adjusted that the blood pressure is maintained at a given height regardless of the volume or character of the blood within the limits demanded by the transfusion of 1000 cc. of blood. From the well-known tendency to hypertension in cases of polycythemia vera, it may be assumed that a certain limit cannot be exceeded.

It may be concluded, therefore, that transfusions of blood in Bright's disease have no effect upon the blood pressure, no matter what the initial level of arterial tension may be. This is of considerable importance in Bright's disease as many of the cases in which the indications for transfusion are particularly urgent, may be subject to a marked degree of hypertension.

The Effect of Transfusion of Blood Upon the Kidney. I. In Patients Without Bright's Disease. The transfusion of blood is a comparatively safe procedure and is hardly ever associated with fatal complications. Bernheim² reported 800 transfusions, for various conditions, in which there were four deaths brought on by hemolysis. In these operations, performed thirteen years ago or more, the preparatory steps for grouping and compatibility were evidently not carried out as well as they are today. Ottenberg³ refers to anuria after transfusion as an exceedingly rare occurrence. Blain⁴ calls attention to the favorable results obtained in 3000 transfusions. Brines⁵ notes the very low incidence of serious reactions during or following transfusions; in his series of 4000 transfusions there were two fatalities and several severe nonfatal reactions. Brines⁵ believes that such reactions are more common when nephritis is present. He cites three instances among 4000 transfusions in which oliguria or anuria occurred with an elevation of the blood urea. There is, however, no proof that nephritis antedated or was the particular cause of these sequelæ. His reference to Blain⁴ in support of his contention is somewhat puzzling since Blain,⁴ in his article, does not mention nephritis. Individual instances of anuria following blood transfusions are reported by Goormaghtigh,⁶ Curtis,⁷ Bancroft,⁸ Oliensis⁹ and Witts.¹⁰ In all of these fatal or severe post transfusion reactions, either hemolysis or anaphylactic shock appeared to be the cause for any complicating effect upon the kidney; the anuria, the hemoglobin infarcts of the kidney and the few instances of tubular nephritis may be explained in this way.

The Effect of Transfusion of Blood Upon the Kidney. II. In Bright's Disease. Transfusions of blood have been carried out in

cases of Bright's disease by a number of clinicians without apparently damaging the kidney in any way. Bell¹¹ reported an instance of relief of anuria in an eclamptic primipara, aged twenty-four years; after a transfusion of 500 cc. of blood the patient became rational in three hours, within sixteen hours 50 ounces of urine were eliminated and in the succeeding twenty-four hours 71 ounces of urine were voided. Ramsay¹² found improvement after transfusion in a case of nephritis with anuria. Ottenberg³ carried out a large number of transfusions on individuals with diseased kidneys and several individuals with one kidney, none of whom showed any untoward effects. Wearn, Warren and Ames¹³ transfused 4 cases of secondary anemia accompanying advanced nephritis without experiencing any difficulties. Martin¹⁴ believes that transfusion overcame oliguria in a seven-year-old boy with edema and albuminuric retinitis. Epstein,¹⁵ and later Clausen,¹⁶ performed transfusions in cases of nephrosis (parenchymatous nephritis) and did not note any unfavorable results upon the kidneys. Burmeister,¹⁷ by alternating venesection and transfusion of normal blood in dogs poisoned by bichlorid of mercury, found less extensive changes in the kidneys as compared to control animals in which this form of treatment was not carried out. Bowers and Trattner¹⁸ report marked improvement in a boy, aged eleven years, with very severe acute nephritis (blood urea as high as 319 mg. per 100 cc.) after decapsulation of the kidneys followed by 4 venesections and transfusions of blood. It is exceedingly difficult to estimate the value of any therapeutic measure in the treatment of acute nephritis as such patients have a very distinct tendency to recover from their acute—so-called uremic or preuremic—symptoms. However, it is permissible to conclude from the findings of Bowers and Trattner¹⁸ that transfusions do not damage the kidney in the severest possible type of acute nephritis.

In the present series of transfusions of blood in Bright's disease there were only 2 cases (Tables III and IV) in which the introduction of blood could possibly be thought to have had an ill effect. The transfusion of blood in the patient whose data are given in Table III was carried out at a time when there was a terminal progressive oliguria which, apparently, was not influenced either favorably or unfavorably by the transfusion. The case shown in Table IV was the victim of a hemoglobinuria; this, apparently, did not influence the existing oliguria to any great extent; however, the blood urea N increased enormously; no evident symptoms resulted from this extremely high concentration of urea in the blood. This patient's death was inevitable and it was neither hastened nor retarded, in our opinion, by the transfusion.

From the literature and our own experience, it would appear that anuria following transfusion may occur. This anuria is not particularly frequent in cases of Bright's disease; in fact, a cessation

of the formation of urine has not been noted in this condition. On the contrary, it is stated by several authors that in Bright's disease the elimination of urine is not interfered with but may even be

TABLE III.—NEGATIVE EFFECT OF TRANSFUSION IN TERMINAL UREMIA.

Date. 1919.	24-hour vol. urine, cc.	Blood urea N., mg. per 100 cc.	Remarks.
Jan. 1-10	2070-4010	37	
11-20	1170-2940	70	
21	2010		
22	2160		
23	1260	136	
24	930		
25	1275	156	
26	1140		
27	600		
28	1125	160	Blood transfusion, 400 cc.
29	1280		
30	330		
31	450		
Feb. 1	750		
2	180	..	Died.

H. L., male, aged twenty-one years, secondary contracted kidney with terminal uremia. Transfusion of blood by the syringe method in this case did not serve to ward off uremia. The oliguria which may, on casual observation, be thought to have been brought about by the transfusion evidently was definitely making itself felt for about four weeks previously; this is shown, not only by the diminishing quantities of urine, but also by the progressive increase in the blood urea N, indicating that the compensatory polyuria was failing.

TABLE IV.—NEGATIVE EFFECT OF TRANSFUSION IN TERMINAL UREMIA.

Date. 1924.	24-hour vol. urine, cc.	Blood urea N., mg. per 100 cc.	Remarks.
Oct. 12	152	Retention uremia present; transfusion (Unger method) two weeks ago
14	300		
15	680	..	Blood transfusion, 700 cc.
16	540		
17	90	380	
18	200		
19	190	357	
20	220	345	
23	Died.

P. D., male, aged forty years, secondary contracted kidney and terminal uremia. In this case, oliguria, following the transfusion of 700 cc. of blood by the direct method, was present before the transfusion was resorted to; hence, transfusion cannot be regarded as bringing about the diminished amount of urine any more than it could in the case charted in Table III. The marked increase in the blood urea N following the transfusion is noteworthy. This was evidently brought on by destruction of red cells since there was a distinct hemoglobinuria associated with the rise in the blood urea N. No evident symptoms resulted from this extremely high concentration of urea in the blood.

stimulated by the transfusion of blood. Diminished kidney activity after transfusion appears to occur only as the result of various factors induced by incompatibility of the blood of the donor with that of the recipient. Anaphylactic phenomena and hemoglobinemia may be cited as the most prominent causes. The effect of these would seem to be the same in normal persons as in those suffering with Bright's disease. The existence of Bright's disease, therefore, should not be regarded as a contraindication to transfusions of blood.

The Relation of Transfusion of Blood to Uremia in Bright's Disease. Transfusions of blood do not alleviate the symptoms of uremia brought on by renal insufficiency, nor do they, apparently, postpone the onset of uremia, when they are resorted to some months previous to the fatal onset brought on by the retention of urinary excretory products. This has been the experience of many clinicians and is ours as well; this is illustrated in Tables III, IV, V and VIII. The procedure of first bleeding patients who are suffering with retention uremia, and subsequently transfusing them with a corresponding amount of blood, has proved itself of no value in a considerable number of cases and this, we believe, is the universal experience. There may be one exception to this statement as illustrated by the experience of Burmeister¹⁷ on dogs. As previously mentioned, he found less extensive changes in the kidneys of dogs poisoned by bichlorid of mercury, when alternating venesection and transfusion of normal blood was resorted to.

There is an idea among many clinicians that transfusions of blood may be harmful in those cases of Bright's disease in which the blood urea N is elevated. Boyd¹⁹ reports transfusions in two such instances and finds that the patients were benefited and not harmed. We have never hesitated to carry out transfusions on patients who gave evidences of nitrogen retention in the blood. The results, with the exception of those to be mentioned in the next paragraph, have been uniformly without untoward effects. Records are given in Tables V, VI and VII of patients whose blood urea N was 63, 54 to 61 and 45 to 27 mg. of urea N per 100 cc. of blood, and where the transfusions of blood did not influence the quantity of urea in the circulation. It is our opinion that when the blood urea is very high, in such instances as given in Table III, the effect of transfusion on the blood chemistry is negligible.

Occasionally, with the production of hemoglobinemia, that is, a destruction of the red blood cells, the blood urea may increase enormously. We have seen this occur on two occasions, one of which is illustrated in Table IV. In this patient, the blood urea nitrogen rose from 152 to 380 mg. per 100 cc. after transfusion. This reaction, presumably, is due to some deficiency in the adaptation of the blood of the donor to the recipient. As previously mentioned, it is of rare occurrence and as the methods of matching

bloods are perfected, it grows even less frequent now than in the past. It is satisfactory to know that these huge increments of blood urea are apparently not productive of symptoms; they seem to have no effect upon the patient nor do they aggravate the uremic signs. This is in accord with the growing belief that urea in itself is not the toxic substance responsible for uremia.

It may be concluded that transfusions of blood are not contra-indicated in uremic states but that no aid for the alleviation of this condition can be expected from them.

The Value of Transfusions of Blood in Treating the Secondary Anemia Occurring in Bright's Disease. Secondary anemia is the invariable accompaniment of severe renal insufficiency as shown by Brown and Roth,²⁰ by Ashe²¹ and by Wilbur and Brown.²² This condition may assume such severity as to invalid the patient and, what is equally important, it may be the sole cause for weakness and ineffectiveness of the sufferer from Bright's disease. Such patients derive great benefit from the administration of blood by transfusion. We have used this form of treatment extensively and have never found it to produce any harmful results. The patient treated in Table V showed a moderate anemia at the time of his first trans-

TABLE V.—NEGATIVE EFFECT OF TRANSFUSION IN TERMINAL UREMIA WITH ALLEVIATION OF ANEMIA.

Date.	Hb., per cent.	R.B.C., millions.	Blood urea N., mg. per 100 cc.	Blood transfu- sion, cc.	Remarks.
1925.					
May 27	70	4.992	45		
1926.					
Mar. 10	65	3.200	63		
24	850	
29	78	4.480			
Sept. 13	50	2.240	63		
15	700	
21	72	3.944	..	700	
28	58	3.096	77	..	First signs of uremia.
Oct. 7	85	..	Uremia.
Nov. 1	21	1.260	259	..	Uremia.
2	Died.

A. S., male, aged thirty-seven years, secondary contracted kidney, renal insufficiency, hypertension. Transfusions of blood served to alleviate the anemia; they produced no untoward symptoms; they did not prevent a fatal termination from retention uremia, though they doubtlessly added much to the happiness and the effectiveness of the last eight months of the patient's life.

fusion. His anemia and the symptoms dependent upon it were relieved. Six months later it was found necessary to repeat the procedure since, as is almost invariably the case with a marked renal insufficiency, the anemia was progressive. However, the life of this individual was made worth while for a period of about six months before the terminal uremia manifested itself. A similar

finding is shown in the case the details of which are given in Table VI. The additional point which may be stressed here is that in this individual the anemia had progressed so far (hemoglobin 39 per cent, red blood cells 1,355,000) that a fatal termination would

TABLE VI.—BENEFICIAL EFFECT OF TRANSFUSION ON ANEMIA.

Date.	Hb., per cent.	R.B.C., millions.	Blood urea N., mg. per 100 cc.	Blood transfu- sion, cc.
1926.				
Nov. 18	80	3.900	16	
1927.				
Jan. 18	74	3.632	33	
Mar. 12	77	3.264	19	
Oct. 12	60	3.808		
1928.				
Mar. 6	56	3.456	22	
May 5	59	3.032	29	
Dec. 8	76	3.400	43	
1929.				
Nov. 2	43	2.600	54	
11	39	1.355		
13	39			
14	51	3.056	..	800
15	61	
18	800
19	58	3.912		
22	63	3.400	59	
24	900
25	74	4.688		
Dec. 2	74	4.936		
10	70	4.064	53	
30	70	4.552		
1930.				
Jan. 13	53	3.688	51	
21	52	3.152		
30	56	4.032	55	
Feb. 12	52	3.096	49	
25	42	2.632		
28	1000
Mar. 1	63	2.208		
5	52	3.904		

H. C., male, aged sixty-three years, chronic diffuse nephritis, gout, diabetes mellitus, angina pectoris. For two years a mounting nitrogen retention and an increasing anemia. Transfusion produces no increase in blood urea and benefits the anemia and its associated symptoms. It is obviously impractical in this case to remedy the very threatening anemia (hemoglobin 39 per cent, red blood cells 1,355,000) by high-protein feeding since the blood urea is at a high level and retention uremia would ensue; transfusion of blood is the only solution for temporary relief. The transfusions held the progressive anemia in check for about three months, when it was found necessary to repeat them.

have ensued through the anemia alone unless the transfusions had been carried out. The first series of transfusions in this case held the progressive anemia in check for periods of about three months, when it was found necessary to repeat them. This patient, after

having been threatened with the fatal complication of progressive anemia, was able to carry on his business affairs, to take vacations in the South and to start on a trip to Europe during the ensuing six months.

TABLE VII.—BENEFICIAL EFFECT OF TRANSFUSION ON ANEMIA.

Date.	Hb., per cent.	R.B.C., millions.	Blood urea N, mg. per 100 cc.	Blood transfu- sion, cc.	Remarks.
1929.					
May 17	69	4.232	38	..	Diet throughout contained 40 to 60 gm. pro- tein a day.
24	54	3.110	
29	27	1000	
31	60	3.300	
June 3	60	3.488	
5	62	3.768	43	750	
10	70	3.750	
13	80	4.360	45	750	
Sept. 11	72	4.840	25	..	
Oct. 15	86	5.144	23	..	
Dec. 10	85	4.536	22	..	
1930.					
Jan. 31	85	4.960	18	..	
April 25	85	5.232	25	..	

F. F., male, aged forty-three years, secondary contracted kidney with a moderate impairment of renal function. The progress of the anemia was checked by several transfusions; subsequently this patient did very well with a protein intake of 40 to 60 gm. a day. This case serves to illustrate that an anemia occurring in some forms of Bright's disease may be rapidly, safely and more or less permanently remedied by blood transfusions. When the impairment of renal function is marked (see Tables V, VI) the anemia recurs, whereas if the kidney eliminates the urinary excretory products satisfactorily, the hemoglobin and red blood cells, as in this case, can be maintained at a normal level for an indefinite period.

The above 2 cases give the result of transfusions carried out in the later stages of Bright's disease. When they are resorted to earlier in the condition (Table VII), the results are much more satisfactory. Under these circumstances, the anemia is much more rapidly remedied than it can possibly be by diet and medication, and if the diet is sufficiently high in protein, the blood may be maintained in a normal condition more or less permanently. All of this was accomplished in the case shown in Table VII. This patient had been rendered anemic, weak and an invalid through protein-food restrictions imposed upon him because of albuminuria, hypertension and renal insufficiency. The anemia at the beginning of the observation, it may be noted, was a progressive one, the hemoglobin dropping from 69 to 54 per cent and the red cells changing from 4,232,000 to 3,110,000 within a week. Following the transfusions, not only was the blood brought to an approximately normal level but the progress of the anemia was completely checked. This is in marked contrast to the 2 previous cases (Tables V and VI) where renal insufficiency was very much more marked. It may be that

transfusions of blood given early in chronic diffuse glomerular nephritis, when anemia and the accumulation of nonprotein nitrogen in the blood are just beginning, will prevent the progressive destruction of red cells and furnish a stimulus for the maintenance of a normal level of hemoglobin and erythrocytes. This is a problem that should be investigated very much more thoroughly but it certainly presents possibilities exceedingly worthy of consideration. The patient described in Table VII, six months after the series of transfusions, gradually resumed his arduous duties as a priest, felt strong and well and maintained his hemoglobin and red blood cells at a normal level without difficulty. In any event, the early use of transfusions can do no harm and may be productive of excellent results. It is worth mentioning that in the case, charted in Table VII, the albuminuric retinitis existing at the beginning of the observation, improved to a remarkable degree. Dr. Martin Cohen, who watched the eyes of this patient, said that he had scarcely ever seen a comparable degree of improvement in the retinitis of Bright's disease.

Secondary anemia occurring in the course of Bright's disease may thus be regarded as a very definite indication for the use of transfusions. This is so because the secondary anemia in itself may produce invalidism and because such a secondary anemia cannot be remedied by dietary measures within the limitations necessitated by the coexisting renal insufficiency. In the later stages of Bright's disease, transfusions of blood may be regarded as a palliative measure only, since they relieve the secondary anemia temporarily, but not for very long. If transfusions are used at an earlier period, when renal insufficiency is first beginning to manifest itself and the secondary anemia is not very marked, there may be a chance to remedy the secondary anemia, more or less permanently, and to check its progressive character. We would, therefore, advocate the use of transfusions of blood for secondary anemia occurring in Bright's disease, whether the anemia be mild or severe, whether it occurs early or late in the course of the nephritis. On the whole, the earlier in the course of the disease that transfusions are resorted to, the more satisfactory will be the results obtained.

The Use of Transfusions of Blood for the Elimination of Edema in Bright's Disease. This has been advocated by Epstein¹⁵ in cases of nephrosis. Clausen¹⁶ resorted to transfusions in parenchymatous nephritis with the idea of remedying the secondary anemia and increasing the blood protein. The theory that edema in Bright's disease is largely due to the diminished osmotic pressure of the blood, accompanying the lowering of the blood proteins, is gaining ground and it would seem rational to suppose that transfusions would be of aid in this connection. The only case in which we have given the procedure a thorough trial (Table VIII) did not show any improvement in the anasarca when the hemoglobin and red blood cells were

elevated by means of transfusions from hemoglobin 52 per cent and red blood cells 2,810,000 to 83 per cent hemoglobin and 4,000,000 red blood cells. The subsequent use of transfusions in attempting to maintain the blood at a high level had no further effect. Although the efforts to control edema by transfusion in this case were unsuccessful, we believe that this method of treatment warrants further investigation.

TABLE VIII.—BENEFICIAL EFFECT OF TRANSFUSION ON ANEMIA, BUT WITHOUT EFFECT ON EDEMA.

Date.	Hb., per cent.	R.B.C., millions.	Blood urea N, mg. per 100 cc.	Blood transfusion, cc.	Remarks.
1929.					
Mar. 4	52	2.810	21	..	There was subcutaneous edema and ascites constantly present; these were not influenced by level of hemoglobin and red blood cells.
13	750	
19	50	2.704	
20	750	
23	77	3.700	
30	72	3.680	
April 6	83	4.000	19	..	
15	70	3.720	
29	72	4.150	32	..	
May 6	51	2.960	
15	1000	
Aug. 14	700	
Sept. 11	60	4.000	25	..	
28	60	3.700	
30	500	
Oct. 20	55	2.920	52	..	
28	69	500	
31	500	
Nov. 6	500	
11	68	3.360	Died.
16	

J. B., female, aged thirty-two years, chronic diffuse nephritis of seventeen months' known duration; there was a marked degree of anasarca. Transfusions of blood, though they served to improve the blood, raising the hemoglobin from 52 to 83 per cent and the red blood cells from 2,810,000 to 4,000,000 per c.mm., did not result in a diminution of the fluid in the subcutaneous tissues or the body cavities. The repeated transfusions of blood did not increase the blood urea content nor did they have an untoward effect of any sort; they probably served to maintain life for a considerable period, as this patient could not overcome her anorexia and ate scarcely any food.

Summary and Conclusions. In cases of Bright's disease treated by other clinics or physicians we have noted that transfusions of blood have been resorted to without untoward results; however, many clinicians fear the use of blood transfusions in nephritic patients because of damage that might be induced in the kidneys. This fear seems not to be the result of actual experience but to be based merely on certain preconceived impressions. From our own findings and those in the literature cited above, we believe that anuria and other complications of transfusion are rare and, further-

more, are not more common in cases of Bright's disease than in other conditions. Several instances of nephritis and anuria are quoted, in which transfusions were followed by distinct improvement in the activity of the kidneys; in our experience, transfusions of blood have no distinct diuretic effect and we believe that when an increased output of urine resulted it was due to the recovery of the kidney function independently of the added blood.

Transfusions of blood in Bright's disease do not raise the blood pressure, do not injure the kidneys, and neither relieve nor aggravate uremic symptoms; they furnish the most suitable means of treating the secondary anemia accompanying marked renal insufficiency; in one case of anasarca complicating a chronic diffuse nephritis neither the subcutaneous edema nor the ascites were relieved by raising the hemoglobin and red blood cells to normal levels by means of repeated transfusions. Further studies should be carried out on the last problem before a definite answer can be formulated in regard to it.

The principal indication for the transfusions of blood in Bright's disease is in the relief of the progressive secondary anemia accompanying impairment of renal function. In such cases it is impossible to remedy the condition by a high-protein diet as retention uremia would be a sequel. Transfusions will ameliorate a serious condition for a long period when the kidneys are moderately involved, for a short time only if the renal parenchyma is largely destroyed. Several successive transfusions are, as a rule, necessary to restore the hemoglobin and red blood cells to an approximately normal level. The procedure may have to be repeated at intervals if the secondary anemia recurs.

REFERENCES.

1. Eyster, J. A. E., and Middleton, W. S.: Cardiovascular Reactions to Hemorrhage and Transfusion in Man, *Am. J. Physiol.*, 1924, 68, 581.
2. Bernheim, B. B.: Hemolysis Following Transfusion of Blood, *Soc. Proc. Mississippi Valley Med. Assn., J. Am. Med. Assn.*, 1914, 63, 1785.
3. Ottenberg, R.: Practical Aspects of Blood Transfusion, *Med. Clin. North America*, 1921, 4, 1509.
4. Blain, A. W.: Impressions Resulting from Three Thousand Transfusions of Unmodified Blood, *Ann. Surg.*, 1929, 89, 917.
5. Brines, O. A.: Fatal Post-transfusion Reactions, *J. Am. Med. Assn.*, 1930, 94, 1114.
6. Goormaghtigh, N.: Toxic Action of Blood Transfusions, *Arch. med. Belges*, Paris, 1918, 72, 611.
7. Curtis, A. H.: Anuria Following Blood Transfusions, *Surg., Gynec. and Obst.*, 1920, 30, 627.
8. Bancroft, F. W.: Anuria Following Transfusion: Effect of Decapsulation of Both Kidneys, *Ann. Surg.*, 1925, 81, 733.
9. Oliensis, A. E.: Acute Nephritis Following Transfusion, *Med. J. and Rec.*, 1928, 128, 178.
10. Witts, L. J.: A Note on Blood Transfusion, *Lancet*, 1929, i, 1297.
11. Bell, W. B.: Treatment of Eclampsia by Transfusion of Blood, *Brit. Med. J.*, 1920, i, 625.
12. Ramsay, J.: Transfusion of Blood in Nephritis, *Brit. Med. J.*, 1920, i, 766.

13. Wearn, J. T., Warren, S., and Ames, O.: Length of Life of Transfused Erythrocytes in Patients with Primary and Secondary Anemia, *Arch. Int. Med.*, 1922, **29**, 527.
14. Martin, W. F.: Value of Blood Transfusion, *J. Urol.*, 1922, **8**, 105.
15. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation, *Am. J. Med. Sci.*, 1917, **164**, 638.
16. Clausen, S. W.: Parenchymatous Nephritis: I. As a General Systemic Disorder, *Am. J. Dis. Child.*, 1925, **29**, 581.
17. Burmeister, W. H.: Effect of Extensive Venesection and Transfusion on Kidney Lesions in Severe Acute Mercuric Chlorid Poisoning, *J. Lab. and Clin. Med.*, 1916-1917, **2**, 500.
18. Bowers, C. A., and Trattner, H. R.: Repeated Venesection: Blood Transfusion in Anuria, *Surg., Gynec. and Obst.*, 1924, **39**, 229.
19. Boyd, M. L.: Blood Transfusions in Genitourinary Surgery, *J. Urol.*, 1925, **14**, 253.
20. Brown, G. E., and Roth, G. M.: The Anemia of Chronic Nephritis, *Arch. Int. Med.*, 1922, **30**, 817; The Prognostic Value of Anemia in Nephritis, *J. Am. Med. Assn.*, 1923, **81**, 1948.
21. Ashe, B.: The Hemoglobin Percentage and the Red Blood Cell Count in Bright's Disease, Myocardial Insufficiency and Hypertension, *Arch. Int. Med.*, 1929, **44**, 506.
22. Wilbur, D. L., and Brown, G. E.: The Blood in Lipoid Nephrosis: With Special Reference to the Absence of Anemia, *Arch. Int. Med.*, 1930, **45**, 611.

THE ETIOLOGY OF ERYTHEMA NODOSUM IN CHILDREN.

ITS RELATION TO EARLY TUBERCULOUS INFECTION.

BY LLOYD B. DICKEY, M.D.,

ASSOCIATE PROFESSOR OF PEDIATRICS, SAN FRANCISCO, CALIF.

(From the Department of Pediatrics, Stanford University Medical School, San Francisco, Calif.)

ERYTHEMA nodosum is seen frequently by the dermatologist and internist. The surgeon sees the condition usually because it may be mistaken at first sight for a suppurative skin condition. Because of its frequent association with diseases of the nose and throat it is occasionally observed by rhinolaryngologists. Because of its rare occurrence in the first decade of life it is not often seen in pediatric practice. During the past four years we have observed 8 cases in the Stanford Children's Clinic, an incidence of about 1 case in 900 children, or 0.11 per cent.

Sutton¹ defines erythema nodosum as "an inflammatory disease of the skin which is accompanied by a variable degree of constitutional disturbance, and is characterized by an eruption consisting of a few or several rounded or oval, painful nodules which persist for two or three weeks and then disappear spontaneously." These nodules are usually more numerous over the tibiae, but may appear on the surfaces of the upper extremities as well. The condition is observed more frequently in females, and the usual occurrence is from ten to thirty years of age.

The histologic picture shows foci of cellular infiltration in the corium, and especially in the subcutaneous fat. Inconstant infiltrates are seen in other layers of the corium. The infiltrates are chiefly perivascular and around the glands, consisting of round cells, some multinuclear granulation tissue cells and polymorphonuclear leukocytes. Fibrinous exudates may occur in the subcutaneous fat and occasionally small hemorrhages are also found here. The endothelium in the small vessels is frequently swollen and shows large nuclei.

Mackenzie's work in 1886,² which associated rheumatism and erythema nodosum, was not challenged until Lendon,³ in 1905, suggested a different etiology. He believed this condition to be mildly infectious and a definite clinical entity. He described prodromal, eruptive and convalescent stages. Phlyctenular conjunctivitis was the only prodromal sign which he regarded as pathognomonic.

Symes⁴ supported Lendon's views and also believed that erythema nodosum strongly predisposed the individual to tuberculosis.

Ernberg⁵ made an elaborate study in support of the theory that erythema nodosum is due to a transient hypersensitiveness to tuberculin in individuals recently infected with tuberculosis. He called attention to the similarity of the process to an artificially elicited tuberculin reaction in a tuberculous individual. The agreement is shown clinically by a similar local reaction, general reaction and focal reaction, and the two are very similar histologically.

Comby,⁶ in a study based on 172 personally observed cases, regarded it as an acute febrile disease resembling more an eruptive than an ordinary skin disease. He believed that an almost extinct tuberculosis might become active in its presence because the tuberculous child is particularly susceptible to all infections. He thought that this was the extent of the connection between tuberculosis and erythema nodosum.

Faerber and Boddin⁷ reported 23 cases, in 21 of which the tuberculin reaction was positive. They excluded the possibility of tuberculosis in the other 2 cases. In the 21 children they noticed no unfavorable activating effects on tuberculosis and no progressive tuberculosis followed any of the attacks of erythema nodosum. Nearly all showed heavy hilus shadows by Roentgen ray following the attacks, and several showed definite epituberculous foci near the hilus of the lung.

Robinson⁸ reported 3 cases of erythema nodosum in 3 different members of the same family, living in the same house. In 45 cases Feer⁹ reported no definite joint involvement or endocarditis in any cases. He collected 749 cases from the literature. Endocarditis was found in only 3, indicating the great improbability of an etiologic association with rheumatic infection. Of 403 cases from the literature tested with tuberculin, 384, or 95.3 per cent, gave positive reactions. Under seven years of age, all of the patients

reacted positively. The reactions were usually very strong, even vesicular or necrotic. Various types of tuberculosis were found in this series, bronchial gland tuberculosis being most common. He did not find that the cases ran a more severe course than the usual juvenile infection.

Arborelius¹⁰ considered the eruption as a nonspecific reaction occurring in various infections, recent tuberculous infection predominating in childhood and youth, other infections of various kinds being the usual cause in older persons. A school endemic of erythema nodosum was reported by Wallgren.¹¹ The 18 cases all gave a positive Pirquet reaction and occurred in a class of 32 children. A recently admitted child in this class had well-developed pulmonary tuberculosis. After the second month of the first child's attendance in school, 17 children showed signs of the infection, 12 presenting erythema nodosum and 6 fever but no lung symptoms. Two months later 13 showed evidence of pulmonary lymph gland tuberculosis and 4 presented suggestive lesions. Wallgren¹² also reported erythema nodosum occurring during the course of the initial fever in tuberculous infection in children.

The following cases are reported from the Pediatric Service of Stanford Medical School, all of which show an association of erythema nodosum with a tuberculous infection.

Case Reports. CASE I.—M. W., a girl aged ten years, entered the children's ward with complaint of tender, reddened, swollen areas over lower legs for one week, and over forearms for one day. The past history and family history gave no significant information. Physical examination showed nothing except many tender, reddened or purplish nodules over the legs and forearms, varying in size from 1 to 2 cm. On the leg they were limited to the anterior aspect, over the tibia, and to one over the antero-medial aspect of the right knee. On the forearms they were on both the posterior and anterior surfaces. The admission temperature was 38.6° C. Blood and urine were normal. Intracutaneous tuberculin was strongly positive in all dilutions down to 0.001 mg. In a dosage of 0.01 mg. a tender indurated, reddened nodule was produced, resembling very closely the lesions of erythema nodosum, with a suggestion of vesiculation in the center of the reaction. Roentgenograms of the chest showed a considerable mass of density at the left lung root (Figs. 1 and 2). The patient underwent a normal convalescence, although several additional lesions of erythema nodosum appeared after she was first seen. All lesions gradually faded, and she had no fever except for her first day in the children's ward.

CASE II.—E. K., a girl aged three and a half years, was admitted to the children's ward with a complaint of pain in the abdomen and legs, and loss of appetite, for the past four days. The family history was negative. The past history was unimportant except that the child had had uncomplicated measles, beginning eighteen days before her entrance. Physical examination showed a pale and listless child with a temperature of 101° F. The tonsils were large and reddened and the tongue markedly coated. There were many small shotty palpable lymph nodes in the neck. There was paronychia of the right middle finger. There were present over the tibia several painful, tender, reddened nodules typical of erythema nodosum.

The tuberculin test was strongly positive. Urine and stool examinations were normal. The white blood cells were 14,750 in number with 66 per cent polymorphonuclears, 28 per cent lymphocytes, 5 per cent large mononuclears, and 1 per cent eosinophils. Roentgenograms of the gastrointestinal tract after a barium meal were negative. Roentgenograms of the chest revealed a mass, probably glands, lying to the right of the midline and extending upward from the hilar region. Hilar shadows on each side were extensive (Figs. 3 and 4). This patient had fever as high as 102° F. during her three-day stay in the hospital. Three days after dismissal her temperature was normal, and the abdominal pain had disappeared. There were still present over the shins the fading lesions of erythema nodosum. The patient did not return to us again.

CASE III.—P. G., girl aged three years, reported to the Outpatient Clinic, with complaint of lassitude, nausea, and abdominal pain of one week's duration, and of painful lumps on the legs for one day. The patient had been vaccinated one week previously and had received her third toxin-antitoxin injection against diphtheria on the same day. The family history was entirely negative except for a history of gonorrheal vaginitis in an older sister. Past history was entirely negative. Physical examination revealed a moderately ill child with a temperature of 99° F. rectally and a pulse of 130. There was some mucus discharge from the nose. The tonsils were reddened and showed signs of infection. In the skin over the lower one-half of both tibiae were several raised, reddened, tender nodules, typical of erythema nodosum. Vaccinia was present over the left deltoid. Blood and urine examinations were negative. Cervical smears were negative for gonococci. The tuberculin test was strongly positive. Roentgenograms of the chest showed markedly increased density and presumably large glands in the left hilus (Fig. 5). The child was entirely well in about one week's time, and the skin lesions had disappeared except for some pigmentation. The vaccinia healed normally.

CASE IV.—A. F., a girl aged ten years, entered the children's ward with complaint of reddened, sore areas over the right shin of two weeks' duration, and over left shin, of three days' duration. The child had been going to school and had no other complaints during the two weeks' period. The family history was negative. In the past history there had been evidence of a chronic sinusitis with occasional bronchial spasm (asthma) for the last four years. The tuberculin test was positive four years previously with evidence of moderate inflammation at the lung roots at this time. Examination showed a well-nourished girl with some dental caries. The pharynx was very granular in appearance, with some purulent material on the left posterior wall of the pharynx. There were reddened, tender, indurated areas over both shins, with increase of local temperature over these areas. The blood showed white cells 14,650 in number, with 81 per cent polymorphonuclears, 17 per cent lymphocytes, 1 per cent large mononuclears, and 1 per cent eosinophils. The urine was normal. An intracutaneous tuberculin with a dose of 0.05 mg. was strongly positive. Roentgenograms of the chest showed heavy densities at the right lung root, greatly increased over those showing in previous films. While under observation the patient had no further complaints, no fever, and is entirely well about eight months after being first seen. The skin lesions gradually faded, and disappeared over a further period of two weeks from the first observation.

CASE V.—W. G., a boy aged two and a half years, came to the children's ward with complaint of fever, intermittent vomiting, irritability, and loss of weight, all of one month's duration. About three days before the begin-

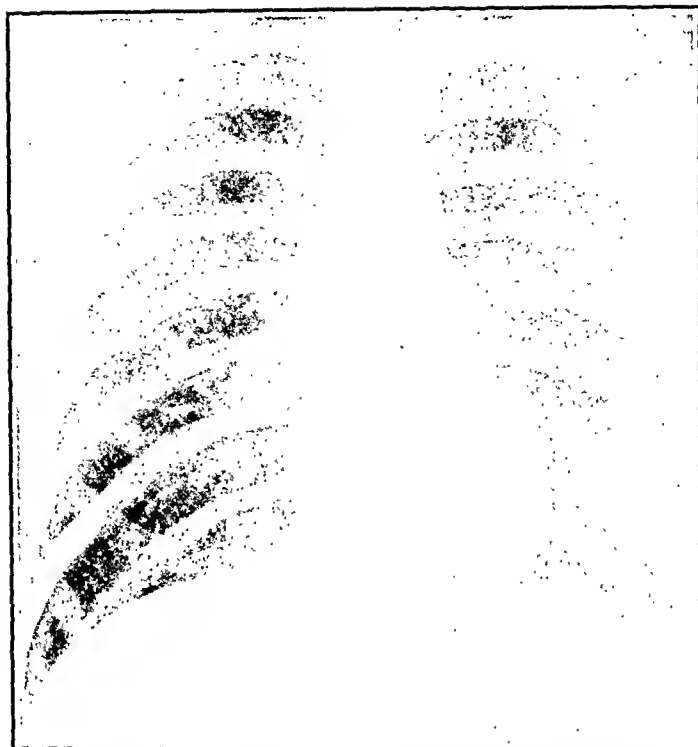


FIG. 1.—Case I. Girl, aged ten years. Roentgenogram of chest, showing probable epituberculous lesion near left hilus.



FIG. 2.—Same as Fig. 1, left lateral view.

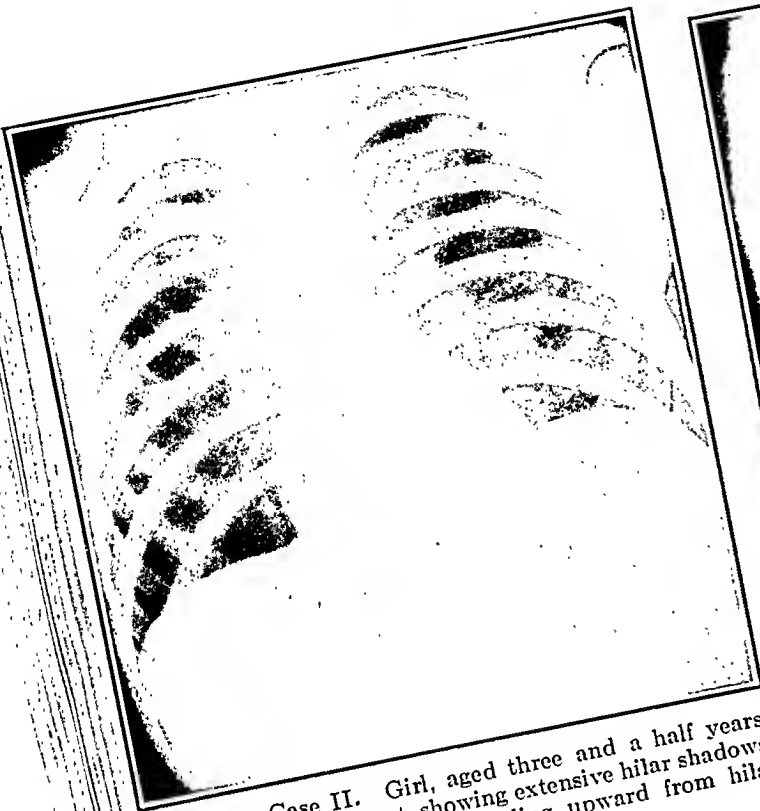


FIG. 3.—Case II. Girl, aged three and a half years. Roentgenogram of chest, showing extensive hilar shadows, and density on right side extending upward from hilar region.



FIG. 4.—Same as Fig. 3, right lateral view.

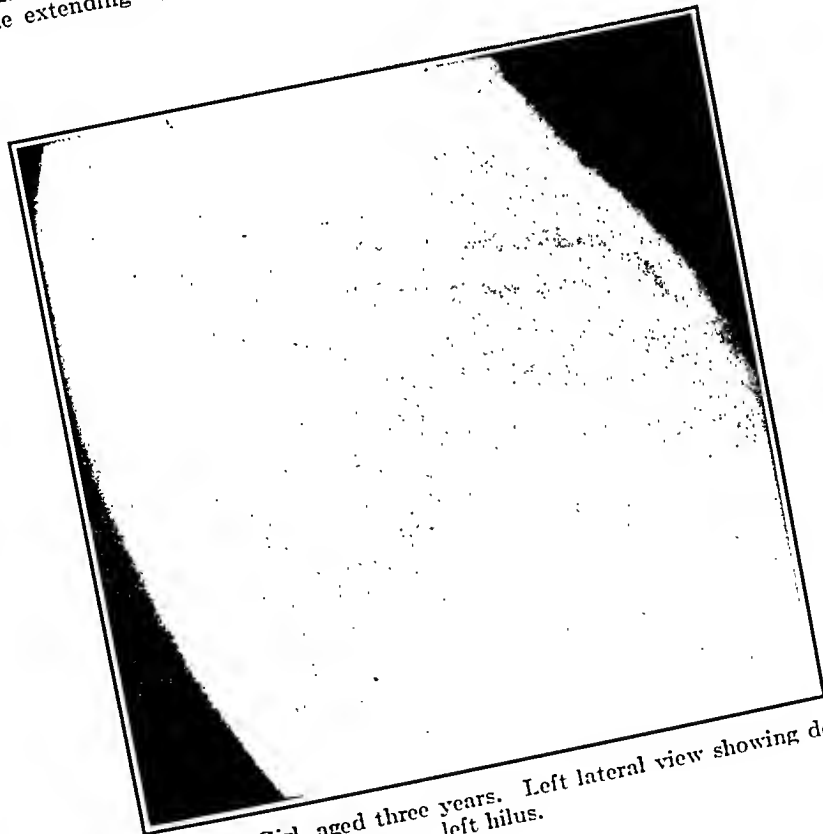


FIG. 5.—Case III. Girl, aged three years. Left lateral view showing density near left hilus.

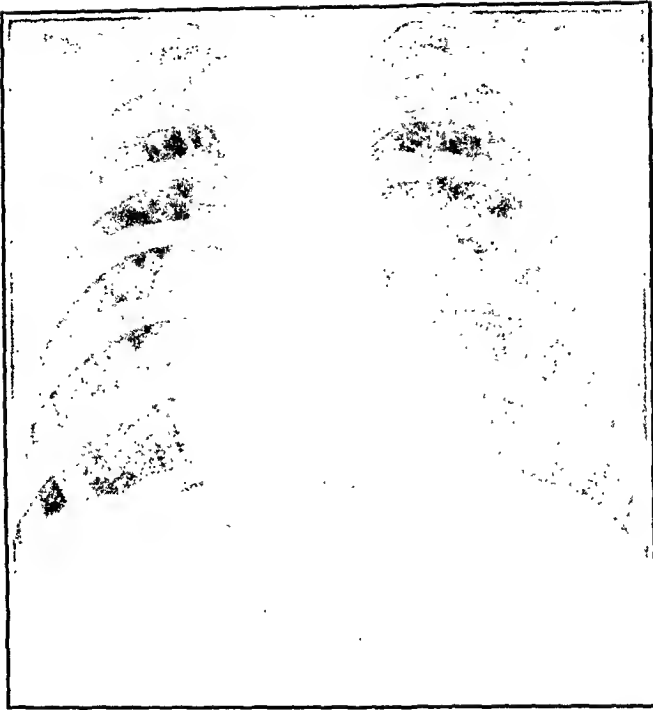


FIG. 6.—Case V. Boy, aged two and a half years. Roentgenogram of chest showing densities near both hiluses.



FIG. 7.—Same as Fig. 6, right lateral view.

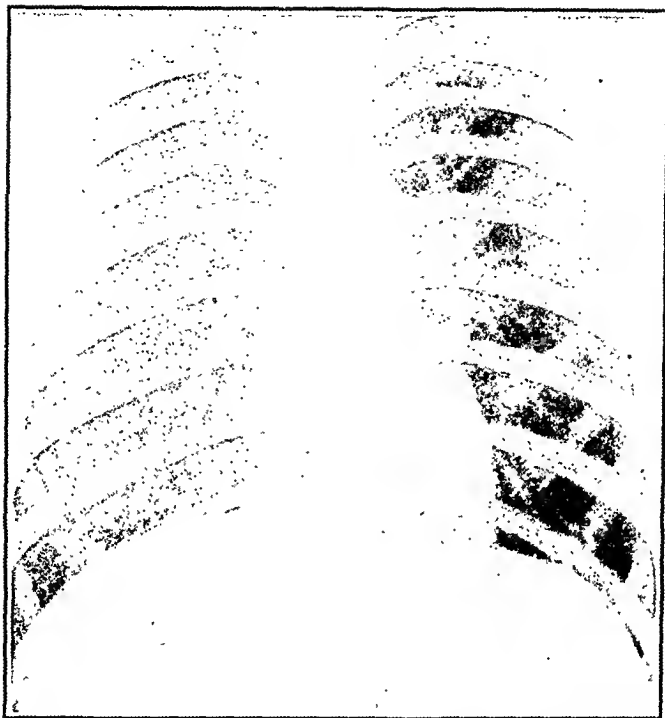


FIG. 8.—Case IX. Boy, aged fourteen years. Roentgenogram of chest, showing heavy hilar shadows and density in the costodiaphragmatic angle on the left side.



FIG. 9.—Same as Fig. 8, left lateral view.

ning of the present illness, the patient had been dismissed from the hospital following a cough, cold, and diarrhea of about one week's duration. The temperature had been 103° F. on the first day of entry, and had returned to normal the next day. There were no important findings in the physical examination, except that the spleen was barely palpable. The blood count was 4640 white cells, with 69 per cent polymorphonuclears, 16 per cent lymphocytes, 8 per cent large mononuclears, and 7 per cent transitionals. Urinalysis was negative. The tuberculin test was negative. During the patient's infancy there had been frequent attacks of acute otitis media, and two attacks of bronchopneumonia. In the family history there was a note of "miner's consumption" in the father. The temperature during the present illness had ranged from 99° to 103.4° F., being highest in the afternoon. Vomiting had followed almost every feeding, and the child's weight had fallen from 40 pounds to 34½ pounds in the one month. Extreme irritability had been present and he had cried at the slightest provocation. He had been much more drowsy than usual. About ten days before the present entry there had appeared several reddened and tender spots over both shins. Physical examination revealed a pale, apathetic child with a temperature of 101° F. The tonsils were very large and ragged, with moderate injection. There was a blowing systolic murmur over the apex. The spleen was palpable 3 to 4 cm. below the costal margin, the liver 2 to 3 cm. Over both shins were crops of brownish and reddish nodules, firm and slightly tender. Brownish pigmentation suggested other faded areas. The hemoglobin was 66 per cent (Sahli). The white blood cells were 17,550 in number, with 80 per cent polymorphonuclears, 15 per cent lymphocytes, and 5 per cent transitionals. Urinalysis was negative. The tuberculin test was very strongly positive, with marked induration. Roentgenograms of the chest showed dense and extensive hilar shadows (Figs. 6 and 7). Blood cultures were negative. The fever resolved after several days in the hospital. The child was kept in bed for one month at home, the weight was regained, and he made an apparently uneventful recovery.

CASE VI.—L. J., a girl aged twelve years, reported to the Outpatient Clinic with complaint of lassitude, fever, and pains in chest, of three days' duration. The father had been actively tuberculous. The child had been a patient in our Clinic for about three years and had reported often for minor ailments and had been treated for a mild chronic sinusitis. Because of her possible contact with tuberculosis she had been tested on three different occasions with 0.1 mg. of tuberculin, always with a negative result. At this visit, which was four months after the last negative test, she was tested with a similar dose and forty-eight hours later the test was strongly positive and there were present several reddened, painful, tender nodules over the shins. The temperature had been 102° F. at home and was 99.2° F. in the Clinic. Otherwise physical examination was negative. The white blood cells were 11,400 in number, with 72 per cent polymorphonuclears, 24 per cent lymphocytes, 2 per cent large mononuclears and 2 per cent transitionals. Roentgenograms of the chest showed enlarged hilar glands. She had no further fever, the erythema nodosum subsided completely in about ten days, and the patient has now been entirely well for two and a half years. About one month after her first positive tuberculin test her father suffered from a pulmonary hemorrhage, his disease progressing rapidly from this point and ending fatally within a year.

CASE VII.—I. S., a girl aged nine years, reported to the Outpatient Clinic because of a vaginal discharge of one week's duration. Father was supposedly an asthmatic with a severe cough. Child had been observed in the Clinic since birth for various minor ailments. Because of failure to gain

and of chronic cough in father, tuberculin test was done five months previously to present illness. There was a strongly positive reaction and roentgenograms of the chest revealed marked hilar densities on both sides. Examination at the present time revealed a markedly underweight child. There was slight discharge but marked reddening about the vaginal and urethral orifices. The left inguinal lymph nodes were tender and enlarged with edema in the soft tissue and slight reddening over the swelling. Several typical lesions of erythema nodosum were present below both knees, and one on the lateral side of the left thigh just above the knee. Unfortunately tuberculin and roentgenographic studies were not done at this time. Both vaginal and cervical smears were negative repeatedly for gonococci. The child is well three years later, but is still underweight.

CASE VIII.—V. B., a boy aged two and a half years, came to the Children's Clinic with complaint of swollen glands in the neck, of three weeks' duration. The family history was negative. There were no complaints other than of the progressive enlargements of the glands of the neck and of slight fever during this time. The patient had been hospitalized at the San Francisco Hospital early in the illness, where the glands were compressed. The tuberculin test was then negative. Examination revealed a moderately pale child with evident lassitude. The temperature was normal. The tonsils were very large and slightly injected. There was a large mass on the right side of the neck about the size of a lemon, firm and not tender. There was no redness nor fluctuation. There was moderate enlargement of the other cervical lymph nodes. The skin was clear. A tuberculin test was performed and when the patient reported in forty-eight hours for reading, there was a marked positive reaction with extensive reddening and induration. There were many small, reddened, indurated nodules in the skin over the arms, thighs, and legs, chiefly on the extensor surfaces, varying in size from 0.5 to 1.5 cm. in diameter. The mother said that these had appeared the night before. The urine was negative. White blood cells were 16,900 in number, with 54 per cent polymorphonuclears, 42 per cent lymphocytes, 1 per cent transitionals, 2 per cent eosinophils, and 1 per cent basophils. Roentgenograms of the chest were essentially negative. Smears from material aspirated from the gland showed acid-fast bacilli, and a guinea-pig inoculated with material showed tuberculosis one month later. The child remained well for two weeks and then suffered from an attack of measles. The glands had to be incised, and are still draining four months later, although the patient is suffering no constitutional symptoms. A roentgenogram of the chest taken three months after the first film was studied showed definite glandular enlargements in the posterior mediastinum causing compression of the trachea.

CASE IX.—D. S., a boy aged fourteen years. This case is from the private records of Dr. Harold K. Faber and Dr. J. G. Bacher, both of whom I wish to thank for permission to include it in this series. The patient was seen by Dr. Faber in consultation with Dr. Bacher, four days after a simple mastoidectomy for acute mastoiditis. Previous to this there had been discharge from the left ear for three weeks. Three months previously patient had complained of night sweats, lassitude, and daily fever of 100° to 101° F., all of which had persisted. Pains in the limbs and joints had followed and roentgenograms of the chest suggested a small effusion on the right side. There had been present over the shins successive crops of reddened, tender nodules for two or three weeks. There was a questionable history of casual exposure to tuberculosis, but not in the home. Examination revealed dullness to percussion at the base of the left lung. In the axilla, on extreme inspiration, pleural friction was heard. The skin was

clear at this time. The tuberculin reaction at forty-eight hours, with a dosage of 0.01 mg., showed an induration of 8 mm. in diameter, with a faint violaceous discoloration around this of an area of 18 mm. by 25 mm. The white blood cells were 16,400 in number, with 75 per cent polymorphonuclears, 23 per cent lymphocytes, and 2 per cent basophils. Roentgenograms of the chest showed density laterally and in the costodiaphragmatic angle (Figs. 8 and 9). These shadows disappeared on subsequent films taken about a month later. Curettings of the mastoid at the time of operation showed granulation tissue in the marrow spaces and in some areas tubercles composed of fibrous tissue cells, some epithelioid cells, and a few multinuclear giant cells. Acid-fast stain failed to reveal any tubercle bacilli. The boy underwent a normal convalescence following the mastoidectomy, all fever disappeared after the fifth day, and he is well fifteen months later.

Discussion. The 8 cases seen in our Clinic represent the total observed over a period of four years. Of the 9 cases in the reported series, 3 occurred in boys, aged two and a half, two and a half and fourteen years, respectively. Six occurred in girls, aged three, three and a half, nine, ten, ten and twelve years, respectively.

In those cases where previous tuberculin tests had been done all were negative except in 2 cases, although at the time of the appearance of the lesions of erythema nodosum, or shortly after, all tuberculin tests were strongly positive with induration, tenderness and erythema which in most cases simulated closely the nodular lesions over the tibiae. In 1 instance the nodules appeared about twenty-four hours after the introduction of tuberculin into the skin.

In only 2 of the cases in this series was a history of exposure to tuberculosis elicited despite the fact that all skin tests were positive.

The roentgenograms of the chest in those cases in which they were taken demonstrated heavy shadows around the hiluses, and in a majority masses of density that were not nodular in outline, but suggestive of consolidation of adjacent pulmonary tissue such as occur in the typical "epituberculous," or "perifocal" lesion. Histologically it is known that these lesions resemble those of erythema nodosum and the positive tuberculin skin reactions.

In one of the cases there was an active tuberculous lesion of the cervical lymph nodes, and possibly in another case, activity in the mesenteric lymph nodes. In the last case of the series a tuberculous focus was demonstrated in the mastoid. In none of the patients observed later did there ever develop any serious tuberculous disease of the chest, but the usual treatment of juvenile tuberculosis was instituted in all those cases which were observed after the appearance of erythema nodosum. In 4 cases there was associated, in addition to a proved tuberculous infection, in one an asthma and chronic sinusitis, in one a vaginitis, probably nonspecific, in another a vaccinia and in another a convalescence from measles.

Pons¹³ observed giant-cell formation in the center of a nodule

of erythema nodosum and Landouzy¹⁴ an acid-fast bacillus in the lumen of a vessel within a nodule. These observations have possibly kept alive the belief shared by some that true erythema nodosum is always related in some way to tuberculosis.

There has accumulated in the literature enough evidence to prove that erythema nodosum may either be caused by or associated with other conditions than tuberculosis. Rosenow¹⁵ has presented evidence to show that the streptococcus is a factor. It has also been reported as associated with smallpox,¹⁶ influenza¹⁷ and other infectious diseases.¹⁰ Possibly in many cases associated conditions influence the allergy, or hypersensitiveness to tuberculin in previously infected tuberculous individuals, so that here tuberculous infection would also be the primary cause. There are also reported cases where sensitiveness to tuberculin has been definitely disproved.^{7,17}

It is safe to state, however, that in children by far the largest number of cases of erythema nodosum is associated with tuberculous infection, and that the infection is usually initial and recent. The statement is more true the younger the individual. There is nearly always an associated hypersensitiveness to tuberculin. The etiologic rôle of tuberculosis becomes less constant with increasing age.

In children under twelve years of age the presence of erythema nodosum should be considered as an evidence of a recently acquired tuberculous infection unless there is definite proof to the contrary, and in its presence the treatment of initial infection should be started.

Conclusion. 1. Erythema nodosum may occur in nontuberculous individuals or in those infected with the tubercle bacillus.

2. The great majority of cases of erythema nodosum in children are associated with a tuberculous infection and most of the infections are initial and recent.

3. Most children who have erythema nodosum exhibit marked hypersensitiveness to tuberculin given intracutaneously.

4. There may be associated, in addition to the tuberculous infection, other conditions which possibly influence the hypersensitiveness to tuberculin.

5. In many cases of erythema nodosum in children epituberculous lesions in the pulmonary parenchyma can be demonstrated by roentgenograms of the chest.

6. In the series reported none of the individuals observed was known to develop a very active tuberculous lesion of the lung.

7. The lesions of erythema nodosum, the epituberculous lesions and the positive skin tuberculin reactions are similar histologically.

8. As erythema nodosum is usually associated in children with early tuberculous infections, proper treatment for the latter condition gives a favorable prognosis as far as tuberculosis is concerned.

BIBLIOGRAPHY.

1. Sutton, Richard L.: *Diseases of the Skin*, 7th ed., C. V. Mosby Company, St. Louis, 1928, p. 139.
2. Mackenzie, Stephen: *On Erythema Nodosum, Especially Dealing with Its Connection with Rheumatism*, Clin. Soc. Trans., 1886, 19, 215.
3. Lendon, A. A.: *Nodal Fever (Febris Nodosa)*, Baillière, Tindall and Cox, London, 1905.
4. Saymes, J. Odery: *The Association of Erythema Nodosum and Tuberculosis*, British Med. J., 1914, i, 909.
5. Ernberg, Harald: *Das Erythema Nodosum, seine Natur und seine Bedeutung*, Jahrb. f. Kinderh., 1921, 95, 1.
6. Comby, Jules: *L'Érythème nouveau chez les enfants*, Arch. d. méd. d. enfants, 1923, 26, 329.
7. Faerber, Ernst; and Boddin, M.: *Erythema nodosum und Tuberkulose, Spontane Rückbildung von Lungeninfiltraten bei Erythema nodosum*, Jahrb. f. Kinderh., 1924, 106, 293.
8. Robinson, D. Gordon: *Erythema nodosum in Members of a Family*, British Med. J., 1926, ii, 1049.
9. Feer, E.: *Zur Aetiologie des Erythema nodosum*, Schweiz. med. Wchnsehr., 1926, 7, 682.
10. Arborelius, Mans: *Erythema nodosum und Infektionskrankheiten*, Acta med. scand., 1928, 68, 151.
11. Wallgren, Arvid: *Eine Schul-Endemie von Erythema nodosum*, Jahrb. f. Kinderh., 1927, 117, 313.
12. Wallgren, Arvid: *Initial Fever in Tuberculosis*, Am. J. Dis. Child., 1928, 36, 702.
13. Pons, J.: *Érythème nouveau d'origine tuberculeuse*, Thèse de Lyon, 1905, p. 57.
14. Landouzy, L.: *Érythème nouveau et septicaémie à bacille de Koch*, Presse méd. Paris, 1913, 21, 941.
15. Rosenow, Edward C.: *The Etiology and Experimental Production of Erythema Nodosum*, J. Infect. Dis., 1915, 16, 367.
16. Tullis, W. L.: *A Case of Erythema Nodosum Following Smallpox*, Lancet, 1927, i, 654.
17. Boganovitch, Vlada: *Five Cases of Post-influenzal Erythema Nodosum*, Arch. Dis. Child., 1930, 5, 56.

ANTISTREPTOCOCCUS SERUM TREATMENT OF PATIENTS WITH RHEUMATIC FEVER.

BY C. H. HITCHCOCK, M.D., CURRIER McEWEN, M.D.,

AND

HOMER F. SWIFT, M.D.,

NEW YORK.

(From the Hospital of the Rockefeller Institute for Medical Research, New York.)

IN the present stage of the therapy of rheumatic fever, any promising remedial agent deserves serious consideration. Except for the antiarthritic and antipyretic drugs, together with the usual measures of strict hospital routine, we have been without means of influencing the course of this infection. It is true that in certain instances these drugs have been reported to exert a favorable effect upon prolonged conduction time,¹ and that occasionally the symp-

toms of carditis respond in as pleasing a fashion as does arthritis; nevertheless common experience has taught that the salicylate effect usually represents an interlude in the course of a disease which, once established, frequently proceeds relentlessly to the production of serious and often eventually fatal lesions. The appearance of subcutaneous nodules in patients under the full influence of salicylate or neocinechophen has been cited as demonstrating the inability of these drugs to prevent the occurrence of more deeply seated damage concomitantly wrought. The importance of the claims of Small,² that the serum developed by him is competent to arrest this damage, can, therefore, scarcely be overestimated; and in view of his results, as well as of the enthusiastic report of Baruffaldi,³ together with the claims of earlier investigators, it has seemed well worth while to investigate further the effects of antistreptococcus serum upon the course of the disease.

In view of the possibility that many types of streptococci may act in the causation of the disease in subjects peculiarly hypersensitive, it seemed reasonable to attempt to determine whether different antistreptococcus sera might not have similar therapeutic effects.

Commercial antitoxic and antibacterial antiscarlatinal serum prepared by the New York City or State Health Departments was employed as antihemolytic streptococcus serum. Through the kindness of Dr. Small, a quantity of S.C.A. (indifferent streptococcus) serum, both bovine and equine, was made available. The equine serum was in concentrated form. For the production of anti-green-streptococcus serum a strain, V110A, originally isolated from an excised subcutaneous nodule, was chosen. With this organism a heifer was immunized by the intravenous route, first with heat-killed vaccine, eventually with large quantities of living culture. After several months' immunization the animal was bled, and about 3 liters of serum of agglutinin titer approximately 1 to 5000 were obtained. This serum, hereinafter referred to as V110A bovine, was stored in the icebox without preservative.

The intramuscular route of administration was always employed, except in one instance when the serum was given intravenously. Suitable intradermal tests with normal sera were always carried out, and, except in two cases referred to below, no serum to which there was evidence of skin sensitiveness was employed.

The evaluation of the effect upon rheumatic fever of any therapeutic measure is a matter of no mean difficulty. The universal application of salicylate therapy has served in a measure to obscure the really tremendous variability in the course of the disease, particularly with respect to such aspects as fever and arthritis. Reference to the older literature⁴ reveals how well this variability was realized before the introduction of antirheumatic drugs. It has been no unusual experience with us to observe marked improvement

in these manifestations, occasionally even complete relief, under expectant therapy alone, within a few days of hospitalization. In the absence of adequately prolonged control periods, such improvement might well have been ascribed to serum therapy, had this been undertaken shortly after the admission of the patient. With regard to severe carditis or to pericarditis, the known tendency of these conditions to pursue more or less self-limited cycles has removed uncertainty to some extent, provided that the treatment has been undertaken sufficiently early in the cycle to warrant the supposition that spontaneous improvement has not been at hand. Even so, however, the uneven course of the disease forbids too dogmatic an interpretation of results.

In this study, emphasis has been laid upon an attempt to secure adequacy of the control period, save only when the condition of the patient has rendered immediate action imperative. In the case of arthritic patients, it seemed desirable to give serum only after several days' observation had apparently established that the disease was running an irregularly continuous course without remissions, or at best with slight and temporary ones; or when, in spite of irregularities in temperature, intensification of the arthritis, with involvement of fresh joints, seemed to indicate the imminence of renewed activity of the infection. Even so, it is with a certain degree of reservation that the occasional improvement of joint symptoms has been attributed to the serum. As regards carditis and pericarditis, the indications have been much clearer; lengthy control periods have usually been precluded, because in each instance the patient has been in the grip of so serious an infection that rapid spontaneous recovery has seemed out of the question. Favorable results observed in this group we have felt might be ascribed largely to the therapy employed, which, let it be noted, was a combination of serum and drug.

The relief only of the major manifestations of rheumatic fever cannot be taken to indicate recovery from the disease, in view of the chronicity of manifestations which may be masked by the use of salicylates. Such items as persisting leukocytosis, subfebrile temperature, failure to gain weight, and variability of the electrocardiogram are now recognized as indicative of persistent infection. No less important, therefore, than adequacy of the preliminary control is minute observation of the patient during the period through which the serum effect may reasonably be expected to persist. This is placed by Small at three weeks or more. It is of course of paramount importance for a proper study that drugs should be withheld during this period. In our study the period of withholding other remedies has only occasionally been so extended, either because of absence of beneficial effects within a few days or because of relapses well before the termination of the prescribed interval. Such relapses, observed not later than two weeks following the treatment, may

reasonably be considered as therapeutic failures regardless of the degree of temporary benefit observed. After all, temporary benefit may usually be rapidly secured with antirheumatic drugs; hence before these can be supplanted by serum, it must be shown that the action of the latter is comparably efficient and reasonably prolonged. With these considerations in mind, we have endeavored to determine as accurately as possible the post-therapeutic course of our patients. The results of the observations have been summarized upon special charts as well as in bedside notes.

To judge critically a single therapeutic agent one should eliminate other favorable influences which arise from hospitalization, adequate nursing, complete rest and proper food; yet these measures are requisite for the patient's welfare. It seems scarcely necessary to emphasize how much more confusion would result if, simultaneously with the serum therapy, were exhibited such drugs as sodium salicylate in arthritis, or bromids or luminal in chorea. Such a study might illustrate still further the efficacy of the drugs, but would be without value with respect to the serum. As far as possible, therefore, we have, except in the case of severely ill patients, abstained from the use of salicylates until satisfied of the failure of the serum. Unfortunately, in a few instances, salicylate was administered at or before the time when the serum effect might have been manifest, and thus the post-serum control period has been inadequate. These few patients, observed in a preliminary study, are included only for the sake of completeness. In the presence of circulatory failure, it has similarly seemed preferable to withhold digitalis insofar as possible. While it is theoretically improbable that this drug would influence an active rheumatic infection, the antipyresis occasionally observed following its administration to patients with congestive failure might confuse the picture were it employed in combination with serum therapy.

Occasionally other irregularities have crept in, as stated in the footnotes to the tables. Attempts at desensitization of two serum allergic patients did not prevent alarming anaphylactoid manifestations after larger doses of serum. Sometimes intradermal tests have been carried out with streptococcal proteins, either during the period of treatment, or shortly before. Although the combined dosage of these proteins never exceeded 0.03 mg., we have subsequently come to realize that this amount is at times sufficient to determine general and focal exacerbations of the disease.

The results are summarized in Tables I to IV, and in illustrative case histories at the end of the paper. In accordance with the advice of Dr. Small, the large doses originally employed were later replaced by smaller ones; consequently it has been necessary to subdivide the tables to follow the alteration of method.

Comment upon these results is interesting. The one patient with chorea to whom the serum was given failed entirely to show evidence

of improvement. A disappointing failure to influence polyarthrititis favorably has been encountered, for among 12 patients with this symptom only 3 showed complete and permanent relief; 2 after S.C.A. serum and 1 after antiscarlatinal. Various degrees of improvement which because of their evanescence can only be classed as failures, were noted following all three sera. Surely this result is eloquent. Were salicylate as ineffectual as serum in this condition, its use would long since have been abandoned. Four patients with carditis showed no evidence of even temporary improvement; in 2 of them the disease progressed steadily to death. In Case 4 a severe carditis developed well within a week of the completion of the serum therapy, and shortly thereafter a crop of subcutaneous nodules appeared. When such nodules were present before the institution of serum therapy, their normal involution showed no acceleration. In the case of pericarditis, however, an attitude of complete pessimism seems unwarranted. It is possible that the combination of drug therapy, given because of the serious character of the symptoms, together with the serum was responsible for the favorable results. Such mixed treatment doubtless confuses validity of conclusions, though it may be argued that drugs alone usually exert only a mild influence upon the course of pericarditis. But the prompt and progressive improvement following the combined therapy in Cases 7, 11 and 17 was probably not attributable entirely to the drug. Although the effect of spontaneous improvement might possibly be evoked in Cases 7 and 11, it is unlikely it would apply in Case 17, where treatment was given at the upturn of the cycle. Obviously, results from such small series as the present cannot settle the point, but can merely indicate possibilities which can be affirmed only after extensive and painstaking observation.

Various reactions quite apart from the usual manifestations of serum sickness have been noted, irrespective of the type of serum employed. The most usual occurrence has been a rise in the temperature, occasionally quite abrupt, at an interval of from three to eight hours following injection. The interpretation of the fever curves is not always an easy matter, because of the innate unevenness of their course; in questionable cases one must judge as well as possible by comparison with the control period. Usually, but not always, a coincident tachycardia was noted, and occasionally there occurred a moderate tachypnea. Such febrile reactions were observed in 57 per cent of the patients, more commonly following the first dose of serum, sometimes in connection with all, occasionally with increasing severity as the course of treatment progressed. Arthritic reactions were noted in 53 per cent of the patients in whom arthritis was the predominant manifestation. These appeared within twenty-four hours of the injection, and consisted either in exacerbations in joints already involved, or in spreads to joints previously unaffected. Such reactions have been described by Small,

TABLE I.—RESULTS WITH S.C.A. SERUM.

Case No.	Name.	Age.	Type of disease.	Day.	Length of control period, days.	Dose (A) in cc.	Reactions (B).	Therapeutic effects.	Remarks.
1*	M.S.	39	Arthritis, carditis, pulmonary	30	1	60 (3) Equ.	Moderate temperature and pulse (1, 2, 3)-5 to 10 hrs.; moderate arthritis (1, 2)-24 hrs.; rales increased (1)-24 hrs.; new murmur (1)-24 hrs.	None	Neocinchophen given after 48 hrs.; prompt relief and progressive improvement.
2**	G. H. (C. R.)	7½	Carditis, circulatory failure	7	6	53 (2) Equ.	None	Slight antipyretic; pulmonary signs appeared on day of second treatment	Became steadily worse; required digitalis; neocinchophen given 2 days after completion of treatment, with moderate improvement only; 2 days later large pleural effusion.
3	J. I.	15	Carditis, nodules, circulatory failure	4th yr.	157	20 (3) Equ.	Shock and chill (1)-30 min.; marked temperature and pulse (1)-8 hrs.	None	Eventually died.
4	S. E. (C. R.)	6	Arthritis, carditis	6	3	5 (2) Equ.	Moderate arthritic (1)-24 hrs.; slight temperature and pulse (2)-3 hrs.; marked respiration (2)-7 hrs.; gallop accentuated (1)-24 hrs.	Marked antiarthritic; otherwise none	Four days later relapse with arthritis and carditis; 1 week later nodules.
5†	A. R.	16	Arthritis, carditis	15	3	10 (3) Equ.	Moderate temperature (1)-7 hrs.; severe temperature; moderate pulse and respiration (2, 3)-6 to 7 hrs.; stupor and delirium (1)-7 hrs.; lasted 3 days; ectopic beats (1, 2)-24 hrs.	Marked antiarthritic; marked antipyretic; marked antitoxic and marked anticarditis	During treatment received large doses of neocinchophen; all improvement could be ascribed to this; severe relapse on drug withdrawal 3 weeks later.
6	A. E.	25	Arthritis, pulmonary	34	5	10 (3) Equ.	Moderate temperature (1, 2, 3)-5 to 11 hrs.; marked pulse and respiration (1)-9 hrs.; new pulmonary signs (1)-24 hrs.	Moderate antiarthritic; slight antipyretic; pulmonary condition unaffected.	One week later temperature became higher, pulmonary condition worse, and relapse of arthritis; responded promptly to neocinchophen.

7††	R. M. (C. R.)	18	Arthritis, pericarditis	22	9	10 (3) Equ.	Moderate temperature and pulse (2)-6 to 10 hrs.; slight arthritic (2)-24 hrs.	Marked marked marked antipyretic	antipyretic; antiarthritic; marked antipericardi- tic	Severely ill; neocinephophen given for 1 week before treatment without effect and continued in small doses during treatment; pleuritic relapse 2 weeks after treatment; thereafter did well.
8	M. Z.	41	Arthritis	19	6	24 (2) Bov.	Slight arthritis (1)-24 hrs.	Antiarthritic, almost complete; antipyretic complete	Permanent; no drug necessary.	
9	C. K. (C. R.)	30	Arthritis	44	5	50 (3) Bov.	Slight temperature (2, 3)-1 to 8 hrs.	Moderate antiarthritic and moderate antipy- retic for 24 hrs.	Thereafter severe relapse; neocinecho- phen given 9 days after completion of treatment; prompt relief.	
10	F. P. (C. R.)	33	Arthritis, earditis	17	2	40 (2) Bov.	None	Marked marked marked antipyretic; antiarthritic; marked antipericardi- tic	After 3 days a pericardial rub appear- ed for 48 hrs.; no drug necessary.	
11†	M. F. (C. R.)	22	Pericarditis, earditis, arthritis	93	9	50 (3) Bov.	Moderate temperature (1, 2)-3 to 4 hrs.; marked pulse and res- piration (1)-3 hrs.; delirium, toxemia, cyanosis (1)-3 hrs.	Marked marked marked antipyretic; antipericardi- tic; marked antitoxic	Neocinechophen begun on first day of treatment on account of serious con- dition; no relapse followed drug with- drawal at end of serum course.	
12††	J. G.	10	Pericarditis, arthritis	5	1	19 (3) Bov.	Moderate arthritis (1, 2)-24 hrs.	Moderate slight heart worse	Neocinechophen given 36 hrs. after completion of treatment; prompt but temporary drug effect, with pericar- ditic and pleuritic relapse after 5 days.	
13§	S. R.	7‡	Chorea	41	37	27‡ (2) Bov.	Slight temperature (1)-8 hrs.; slight pulse (1)-12 hrs.	None	Given 0.01 mg. streptococcus protein i. v. 2 days before beginning treatment.	

(A) Figures in parentheses indicate days over which total dosage given was distributed.

(B) Figures in parentheses indicate dose after which reaction occurred. Periods of time following dashes indicate interval elapsing before reaction was noted.
* Insufficient control and observation periods; included only for sake of completeness. Skin tests with 0.03 mg. streptococcus proteins on day following completion of treatment. Not included in Table IV.

** Observation period of only two days because of rapid deterioration.

† Not included in Table IV.

†† Treatment begun on eleventh day of pericarditis.

‡ Admitted with arthritis only; developed pericarditis under observation; treatment begun on fifth day of pericarditis.

‡‡ Insufficient control and observation periods; included only for completeness. Skin tests with 0.03 mg. streptococcus proteins on first day of treatment. Not included in Tables IV, V and VI.

§ Treatment given during a course of immunization with hemolytic streptococcus protein.

C. R.—For case reports see end of paper.

TABLE II.—RESULTS WITH V110A SERUM.

Case No.	Name.	Age.	Type of disease.	Day.	Length of control period, days.	Dose (A) in cc.	Reactions (B).	Therapeutic effects.	Remarks.
14	M. B.	22	Arthritis	7	3	40 (2)	Slight arthritis (1)–24 hrs.	Slight antiarthritic and slight antipyretic, 20 hrs. after first dose.	Thereafter much worse.
15	H. C.	19	Carditis, arthritis, nodules	35	8	40 (2)	Moderate temperature (1, 2)–4 to 8 hrs.; cyanosis and restlessness (1)–12 hrs.	Slight antiarthritic for 4 days; otherwise none	Became progressively worse; fibrillated after 2 weeks; neocinchophen given after 5 days.
16*	J. S.	48	Arthritis	30	1	45 (2)	Moderate temperature and pulse (1)–4 to 8 hrs.; dyspnea and cyanosis (1)–4 hrs.	Antiarthritic, almost complete, for 6 days	No antipyretic effect; after 6 days severe relapse, controlled only by full doses of neocinchophen.
17†	A. P. (C. R.)	8	Pericarditis, pulmonary	18	11	20 (2)	None	Marked antipyretic; cardiac and pulmonary condition improved gradually	Received neocinchophen 2 gm. daily during treatment; 1 week later rub returned for 3 days, then settled down into subacute course.
18	R. F.	33	Arthritis	43	5	47 (3)	Marked arthritis (1, 2, 3)–24 hrs.	Worse	Three days later given neocinchophen with prompt improvement.
19	W. F. (C. R.)	41	Arthritis	26	2	40 (2)	Moderate temperature and pulse (1, 2)–3 to 6 hrs.; slight arthritis (1, 2)–24 hrs.	Marked antipyretic; marked antiarthritic	After four days severe febrile and arthritic relapse, yielding promptly to neocinchophen.
20	I. S.	18	Arthritis, carditis	78	34	50 (3)	Moderate pulse (3)–24 hrs.	None	After 3 days entered upon a moderately severe cycle of fever and arthritis.

(A) Figures in parentheses indicate days over which total dosage given was distributed.

(B) Figures in parentheses indicate dose after which reaction occurred. Periods of time following dashes indicate interval elapsing before reaction was noted.

* Skin tests with streptococcus proteins on first day of treatment.

† Neocinchophen 2 gm. q.d. during treatment.

C. R.—For case report see end of paper.

TABLE III.—RESULTS WITH SCARLATINAL ANTITOXIN.

Case No.	Name.	Age.	Type of disease.	Day.	Length of control period, days.	Dose (A) in cc.	Reactions (B)	Therapeutic effects.	Remarks.
21*	L. B.	48	Arthritis, pulmonary	19	5	55 (3)	Slight temperature (1, 3)—4 to 5 hrs.; moderate pulse (1, 2)—4 to 5 hrs.; moderate arthritis (1, 2, 3)—24 hrs. rales increased (1)—24 hrs.	Slight antiarthritic	Disease apparently on the upgrade when sodium salicylate was given 2 days later.
22†	B. S.	19	Arthritis	23	3	23 (1)	Moderate temperature, 8 hrs.; rash, 24 hrs.; local, 8 hrs.	None at once; after 2 days fever and new murmurs; after a further 4 days pericarditis with effusion.	
23‡	A. S.	30	Arthritis	15	2	16 (2)	Marked dyspnea and cyanosis (2)—5 hrs.; slight temperature and pulse (2)—8 hrs.; marked arthritic (2)—24 hrs.	Slight antipyretic only	Because of poor condition neocinchophen given after 2 days; prompt relief.
24	R. McM.	18	Arthritis	70	8	6 (2)	None	Marked antipyretic; marked antiarthritic	Incomplete recovery; neocinchophen started after fifth day; relapse after 17 days.
25	N. S. (C. R.)	45	Arthritis	27	11	10 (4)	Marked arthritic (1)—24 hrs.	Marked antiarthritic, marked antipyretic	Three days later mild relapse of 6 days' duration; thereafter permanent relief.
26§	P. McD.	13	Carditis, arthritis, pulmonary	3	2	10 (3)	Vomiting (1) several hours	Moderate antipyretic, moderate antiarthritic after first dose only; cardiac and pulmonary condition worse	After 2 days given neocinchophen with prompt antipyretic and antiarthritic effect; other conditions improved more slowly but steadily.

(A) Figures in parentheses indicate days over which total dosage given was distributed.

(B) Figures in parentheses indicate dose after which reaction occurred. Periods of time following dashes indicate interval elapsing before reaction was noted.

* Observation period of only forty-eight hours robs case of value. Not included in Table IV.

† Attempt to desensitize a sensitive patient, with unpleasant sequelae. Not included in Tables IV, V and VI.

‡ Desensitization unsuccessful; very severe serum shock. Observation period forty-eight hours only, on account of poor condition of patient. Not included in Tables IV, V and VI.

§ Received unconcentrated serum. Only forty-eight hours' observation period because rapidly becoming worse.

C. R. — For case report see end of paper.

TABLE IV.—SUMMARY OF THERAPEUTIC RESULTS.*

	No. of patients.	S.C.A. serum.		V110A serum.		Scarlatinal antitoxin.		Totals.	
		Success.**	Failure.	Success.	Failure.	Success.	Failure.	Success.	Failure.
Chorea . . .	1	0	1	0	1
Arthritis . . .	12	2	3	0	5	1	1	3	9
Pericarditis . . .	3	2†	0	1†	0	3†	0
Carditis . . .	4	0	2	0	1	0	1	0	4
Totals . . .	20	4††	6	1†	6	1	2	6§	14

* Does not include Cases 1, 5, 12, 21, 22 or 23.

** The term "success" must be accepted with the qualifications expressed in the text.

† These patients received neocinchophen in addition.

†† Two of these patients received neocinchophen in addition.

‡ This patient received neocinchophen in addition.

§ Three of these patients received neocinchophen in addition.

who states that they attack particularly the smaller joints; in our experience, however, the larger ones have been affected about as frequently as the others. Usually there has been subsidence within twenty-four hours, though in Cases 14 and 18 the condition became progressively worse. In Cases 5 and 11 severe toxemia with delirium followed the use of S.C.A. serum. Less common manifestations have included the appearance of a new murmur, numerous ectopic beats, an increase in pulmonary moisture (râles), and chill, vomiting and other phenomena of protein shock. Dosage of serum, whether large or small, has seemed immaterial; in fact, one of the most alarming reactions occurred three hours after an initial injection of 15 cc. of S.C.A. bovine (Case 11), while in another case delirium of three days' duration set in following the use of 3 cc. of S.C.A. concentrated equine (Case 5). In the latter instance a full course of 10 cc. was given over a period of three days, and large doses of neocinchophen were administered; in addition to the delirium, severe febrile and pulse reactions occurred after each injection of serum, and numerous ectopic beats were observed. A dry pericardial rub of forty-eight hours' duration was noted in Case 10, though it did not appear until three days after the last dose, and consequently cannot fairly be attributed to the serum. Tables V and VI summarize these by-effects. Reactions occurring in "serum desensitized" patients have not been included, as the effect of the factor of serum allergy could not be controlled. As warning against serum treatment of such sensitive individuals may be cited, however, a severe asthmatic attack with deep cyanosis in one patient (Case 23), while in another instance severe carditis, with pericarditis and effusion, developed immediately (Case 22).

TABLE V.—REACTIONS: TABULATED ACCORDING TO SERA.*

	S.C.A. serum.	V110A serum.	Scarlatinal antitoxin.	Totals.
Total doses	31	16	11	58
Temperature	17	5	2	24
Pulse	17	4	2	23
Respiration	5	0	2	7
Cyanosis	1	2	0	3
Delirium	2	0	0	2
Arthritis	5	6	4	15
Shock and chill	1	0	0	1
Ectopic beats	2	0	0	2
Restlessness	0	1	0	1
Dyspnea	0	1	1	2
Vomiting	0	0	1	1
Pulmonary signs	2	0	1	3
Gallop accentuated	1	0	0	1
New murmur	1	0	0	1

* Does not include Cases Nos. 12, 22 or 23.

TABLE VI.—REACTIONS: LISTED ACCORDING TO PRINCIPAL CONDITION.*

	Chorea.	Arthritis.	Pericarditis.	Carditis.	Totals.
Number of patients	1	15	3	4	23
Temperature	1	8	2	2	13
Pulse	1	8	2	1	12
Respiration	0	3	1	0	4
Cyanosis	0	1	1	1	3
Delirium and toxemia	0	1	1	0	2
Arthritis	0	8	1	0	9
Shock and chill	0	0	0	1	1
Ectopic beats	0	1	0	0	1
Restlessness	0	0	0	1	1
Dyspnea	0	1	0	0	1
Vomiting	0	0	0	1	1
Pulmonary signs	0	3	0	0	3
Gallop accentuated	1	1	0	0	1
New murmur	0	1	0	0	1
Patients without reaction— under drug	1	...	1
Patients without reaction— not under drug	2	...	1	3

* Does not include Cases Nos. 12, 22 or 23.

The occurrence of reactions seems to bear no relationship to subsequent improvement or to its permanency.

The danger of such reactions may perhaps be decreased by the simultaneous use of salicylates, which, however, as pointed out above, scientific precision usually forbade during this study. In the few instances cited, in which the condition of the patients seemed to prohibit delay, these drugs have rarely proven efficacious in warding off the reactions, and on one occasion truly alarming symptoms developed (Case 5).

Discussion. Generalizations based on a comparison of the three sera used in this study are hardly justifiable in so small a series of cases. The three different sera were made in as many different laboratories by different methods of immunization, and it is not improbable that had 3 horses or cows been immunized with the same strain of streptococcus by different methods similarly varying results would have been obtained. Hence it is probably better to disregard the effects from any particular serum and discuss them all together. It is, however, noteworthy that comparable symptoms, both favorable and unfavorable, were observed following all three types of serum; and it is not without interest that similar effects were observed over twenty-five years ago by Menzer,⁵ Schmidt⁶ and Sinnhuber,⁷ when a polyvalent antistreptococcus serum prepared by the former was employed. All of these observations lead to the conclusion that any beneficial therapeutic effect observed must be dependent upon some other factor than a specific antitoxin against a hypothetical toxin elaborated by one strain of streptococcus.

Indeed, Menzer,⁸ although for years an active proponent of a specific antitoxic action of serum, later attributed the beneficial effect to nonspecific protein therapy ("Reiztherapie"), and hence gave up the use of serum in favor of streptococcus vaccines. His abandonment of serum would appear one of the strongest arguments against its use. But the enthusiastic reports of Baruffaldi,³ and the observations of Toogood⁹ and Barach¹⁰ with antiscarlatinal serum, together with Small's claims, made necessary a further study, with the results as above recorded.

From a theoretic viewpoint it may be asked: were any effects, either beneficial or otherwise, constantly attendant upon the application of these sera, which might be ascribed to their antistreptococcus qualities rather than to their actions as foreign proteins? In the absence of a control group treated simply with normal horse or cow serum a satisfactory answer to this question cannot be given.

Small¹¹ bases part of his hypothesis of the pathogenesis of rheumatic fever upon focal reactions in the small joints, together with general reactions following serum treatment. He attributed these reactions, which he designates as exudative, to a union of streptococcus antiprotein, contained in all antistreptococcus serum, with streptococcus protein, which he thinks is present in the tissues. Similar focal reactions have been reported following tuberculin treatment¹² and other forms of nonspecific protein therapy; hence this hypothesis demands further testing.

From another theoretic viewpoint one would not expect marked specific beneficial action to follow antistreptococcus serum therapy in rheumatic fever, for it is not of the general type of disease which responds favorably to serum. Usually rheumatic fever is not an acute disease like diphtheria, tetanus, or scarlet fever, but a sub-

acute or chronic infection resembling tuberculosis or syphilis in many of its features.^{13, 14}

If a hypothetic toxin or some peculiar bacterial fraction or autolysate is responsible for the various manifestations of the disease, these substances are elaborated in varying amounts and intensity over long periods; hence it is improbable that a serum effect, which at best can be of only short duration, would be ultimately successful. Indeed, Small early recognized this possibility and recommended, in addition, a form of active immunization by repeated subcutaneous injections of an extract of *Streptococcus Cardioarthritidis*. He has reported better results with the use of this combined method than with the serum alone.

But in spite of these theoretic objections, if consistent improvement followed the application of antistreptococcus serum, one would be compelled to modify his theory, and utilize the serum. Our observations, together with those of Hill¹⁵ and Wilson,¹⁶ however, lead to the conclusion that antistreptococcus serum has no permanent antirheumatic influence, and that acute antipyretic, antiarthritic and antitoxic effects can be more certainly obtained from salicylates or neocinchophen. Whether the favorable effects which followed a combination of these drugs with serum in a few cases of pericarditis were anything more than fortuitous is open to discussion.

Of this one can be certain: that antistreptococcus serum in no way replaced the long-established therapy of rheumatic fever, nor does it apparently add enough to warrant its universal adoption. In our experience the unpleasant reactions sometimes attendant upon its application have not been outbalanced by a reciprocal certainty of therapeutic benefit.

Case Reports. CASE 2.—G. H., male aged seven and a half years, admitted March 5, 1928, to the service of Dr. Rivers because of chicken pox developing during the course of rheumatic carditis present at least since November, 1927. March 9, following the subsidence of the varicella, a further rheumatic cycle appeared. By March 14 there were present: temperature 104°, pulse 130, respirations 50, gallop rhythm, mitral and aortic regurgitation, positive Broadbent sign, severe precordial pain and hyperesthesia, hepatic enlargement with severe right upper quadrant pain. On this day S.C.A. concentrated equine serum was given intramuscularly in 3 doses of 10, 8 and 10 cc. respectively, between 12 noon and 9 p.m. No immediate reaction occurred. March 15 no evidence of improvement; similar serum was given, 15 cc. at 10 a.m., and 10 cc. at 6 p.m. During this day the temperature declined to 101.2° and the respiration to 40; no change in pulse rate. During the next three days no improvement; but dullness, bronchial breathing and bronchophony appeared at the angle of the left scapula, and there was cough with mucoid sputum. Neocinchophen therapy was instituted, and resulted in temporary improvement in the cardiac and pulmonary conditions.

CASE 4.—S. E., male, aged six years, admitted February 15, 1929, on the third day of his second attack of rheumatic fever; temperature, 102.4°;

pulse, 130; respirations, 24; moderately severe polyarthritis, tonsillar infection, enlargement of heart to left, mitral systolic murmur heard throughout left axilla and left back, accentuated and split P_2 , white blood cells 22,000. Under expectant therapy, temperature and pulse remained elevated; February 18, spreading of arthritis and a questionable gallop; 2.5 cc. of S.C.A. concentrated equine serum was given intramuscularly at 2 P.M. At this time temperature was 104.4° , pulse 130, and these levels were maintained throughout the day. February 19 A.M. the arthritis was much more severe; no new joints involved; there was a loud gallop; 2.5 cc. of the same serum was given at 11 A.M. Five hours later the temperature had risen from 103.4° to 104.4° and the pulse from 106 to 128. These levels were maintained throughout the day. The respirations rose to 60. February 20 A.M. the temperature was 102.4° , pulse 110, respirations 36, but during the day rose to 104° , 130 and 62, respectively. Arthritis considerably improved. February 21, fever much the same, though the pulse failed to pass 110° or the respirations 42; the gallop persisted; the patient was free from arthritis, but after a further two days this reappeared and the following morning (February 24) was so severe that neocinchophen administration was begun. At no time during this interval did the temperature fall below 102° , and the pulse constantly ranged from 104 to 120 with the gallop unchanged. At the time of the arthritic relapse the pulse rate increased rapidly, the area of cardiac dullness increased, the murmur became harsh and grating, and the cardiac action became quite tumultuous. The respiratory rate rose to 70, with grunting expiration, and fine râles were heard in the left chest posteriorly. There were no signs of consolidation either by direct examination or by Roentgen ray. The carditis and pneumonitis were at their height February 28, nine days after the completion of the serum course. Four days later a small crop of subcutaneous nodules appeared. The carditis ran a moderately severe course with subsequent marked improvement.

CASE 7.—R. M., male, aged eighteen years, admitted January 2, 1929, on the thirteenth day of his first attack of rheumatic fever; temperature, 105° ; pulse, 120; respirations, 36; cyanosis, severe toxemia, mild polyarthritis, small adherent tonsils, precordial hyperalgesia, cardiac enlargement, heart sounds muffled at the apex and over the precordium, loud pericardial friction rub, dullness in lower left axilla, also over the left lower lobe posteriorly merging into flatness at the base, with decreased tactile fremitus, bronchovesicular breathing and numerous moist and fine râles, merging into suppression at the left base, Grocco triangle to the right; roentgenograms indicative of pericardial and pleural effusions. Because of the critical condition neocinchophen was administered; this resulted in a moderate but very fleeting improvement; by January 11 the condition was very serious, and because of intolerance it had become necessary to reduce greatly the dosage of drug. At 2.45 P.M. of this day 5 cc. of S.C.A. concentrated equine serum was given intramuscularly. No reaction occurred. At 2 P.M. temperature was 102.8° , pulse 120; these levels were maintained until 8 P.M., after which a steady decline ensued. January 12 noon, temperature was 99.8° , pulse 104. No subjective or objective improvement was apparent. At 10.45 A.M. 5 cc. of serum was given. By 4 P.M. temperature had reached 103.4° ; at 8 P.M. the pulse was 128. Shortly thereafter a decline in both occurred similar to that of the day before. January 13, distinct exacerbation of the polyarthritis; otherwise the general condition was the same, except that the steady loss of weight was checked. Thereafter steady improvement occurred, which by January 18 seemed complete, except for persisting leukocytosis and a small pleural effusion. The latter disappeared following a sharp febrile episode between January 28

and February 1. Drug withdrawal a few days later was followed by uneventful recovery.

CASE 9.—C. K., male, aged thirty years, admitted May 9, 1929, on the fortieth day of the first attack of rheumatic fever; temperature 104° , toxemia, moderately severe polyarthritis, tonsillar infection, short systolic murmur along the left sternal border, palpable spleen. During five days control period fever continued, arthritis spread rapidly, the heart sounds became progressively softer and more distant, and there was steady loss of weight. On May 14, fever slightly lower but arthritis again spreading; 15 cc. of S.C.A. unconcentrated bovine serum was given intramuscularly at 2 P.M. No detectable reaction; the maximum temperature, 102.4° at 6 P.M., was only 0.6° higher than at 2 P.M., May 15, temperature had dropped to 100.2° , the arthritis was much improved and the heart sounds were clearer and louder. At noon 15 cc. of serum was given. At 8 P.M. a sharp rise in temperature to 101.8° occurred, thereafter an equally sharp decline. May 16, the arthritis had largely disappeared, heart sounds quiet and strong, murmur faint, temperature 100.2° . At 2.10 P.M. 20 cc. of serum was given. At 8 P.M. the temperature rose sharply to 101° , then quickly fell. May 17, arthritis in the right arm worse, and by evening the temperature was 101° . On May 19 the temperature once more began to rise and arthritis reappeared; by May 24 the patient was helpless, toxic, rapidly losing weight, with fever above 103° . Neocinchophen promptly controlled the fever and arthritis, and on its discontinuance on June 3 only a moderate shoulder stiffness persisted.

CASE 10.—F. P., male, aged thirty-three years, admitted December 5, 1928, on the fourteenth day of the first attack of rheumatic fever; temperature 103.4° , pulse 104, severe and widespread polyarthritis, ragged tonsils, reddened anterior pillars, palpable tonsillar nodes, soft systolic murmur at apex; leukocytes 27,000. During forty-eight hours of expectant treatment he became steadily worse, temperature hovering at 104° and pulse at 120; *P-R* interval 0.21. December 7, precordial tenderness and gallop rhythm. At 2 P.M. he was given intramuscularly 20 cc. of S.C.A. unconcentrated bovine serum without demonstrable reaction. A steady decline in fever occurred reaching 101.6° at 10 A.M. the following day. Pulse rate and arthritis unaffected, precordial tenderness still present, gallop rhythm less definite; *P-R* interval 0.20. December 8 at 12.15 P.M. he was given 20 cc. of the same serum without demonstrable effect. December 9 fever ranged between 101.4° and 102.4° , pulse 105 to 115, arthritis slightly improved, gallop doubtful, patient less toxic. December 10, however, definite improvement appeared, and by December 16 the temperature was normal, only arthritic symptoms were tender spots about the larger joints; *P-R* interval 0.18, white blood cells 10,640. Precordial tenderness and gallop had disappeared. The periarticular tenderness persisted until after tonsillectomy; otherwise the patient's course was satisfactory. On December 11 and 12 there was a recurrence of precordial tenderness and a dry-friction rub was heard at the left sternal border at the level of the second and third interspaces.

CASE 11.—M. F., male, aged twenty-two years, admitted June 3, 1929, during the twelfth week of the first attack of rheumatic fever; temperature 100.2° , pulse 120, mild polyarthritis, chronic tonsillar infection, systolic precordial heave, systolic impulse and thrill in second left interspace, cardiac enlargement, precordial pain and tenderness, widely transmitted apical systolic murmur, short mid-diastolic puff medial to apex, systolic murmur at base heard in neck vessels. P_2 accentuated and split, systolic and diastolic crunching sounds at level of second interspace, scattered sub-

cutaneous nodules. White blood cells 9,800. During following week he became steadily worse. June 10, pulse 152, widespread erythema multiforme, mushy and muffled first sound, pericardial friction rub, increase in the size of the heart, bronchovesicular breathing and bronchophony at the angle of the left scapula, white blood cell 18,800; increased weight associated with fluid retention. Because of severity of symptoms neocinchophen was started in full doses without inducing antipyresis or amelioration of symptoms in forty-eight hours. June 12, 15 cc. of S.C.A. bovine unconcentrated serum intramuscularly at 11.30 A.M. At 8 A.M. of this day the temperature had been 101.4°, pulse 136; at noon, temperature 102°, pulse 148; at 2 P.M., temperature 103°, pulse 152. By this time the patient was delirious, restless and required restraining; head retracted and head and eyes turned constantly to the right, violent muscular tremors, heart sounds soft and distant, pulse of poor quality, cyanosis of the extremities. No signs of congestive failure. During the day 0.7 gm. digitan was given, and the dosage of neocinchophen was reduced. By evening temperature and pulse were falling sharply and delirium had vanished. June 13 condition improved, diminution in cardiac size, no precordial pain and little tenderness, no signs of compression of the left lower lobe, sticky râles at both bases; 7.5 cc. of serum was given at 10.30 A.M., and at 3.30 P.M. At 10 A.M. temperature was 100.5°, pulse 132; maximum temperature at 2 P.M., 101.8; pulse 136; no untoward reaction. During the night there was a sharp drop in temperature and pulse, which on the following day failed to pass 100.8° and 110 respectively. June 14, 10 cc. of serum was given at 11.20 A.M. and at 3.30 P.M. without demonstrable reaction. Steady and rapid improvement continued. Drug withdrawal on June 16 was uneventful, and the further course was entirely satisfactory.

CASE 17.—A. P., female, aged eight years, admitted January 10, 1929, on the seventh day of her second attack of rheumatic fever; temperature, 105°; pulse, 140; respirations, 44; marked orthopnea, acute polyarthritis, scarred remnants of tonsillar tissue, anterior pillars injected, tonsillar nodes enlarged and tender, diffuse precordial pulsations, cardiac enlargement, loud pericardial friction rub with synchronous thrill, gallop rhythm; over the left lower lobe dullness with bronchial breathing and bronchophony merging into suppression at the base, diminished breath sounds at the right base, white blood cells 33,600; roentgenogram suggests pericardial effusion. Under neocinchophen therapy steady improvement occurred for a week, with disappearance of arthritis, lowering of temperature, pulse rate and leukocyte count, and retrogression of pulmonary and precordial signs. Complete recovery was not achieved, however, and on January 21 an obvious relapse was under way in spite of drug administration. On this day 10 cc. of V110A unconcentrated bovine serum was given intramuscularly at 3 P.M. without immediate reaction. The temperature peak for the day was 102.8° at 4 P.M. followed by a steady decline; pulse little affected. January 22, patient appeared rather better; 10 cc. of the same serum was given at 2.40 P.M. No demonstrable reaction occurred. The temperature peak for this day was 100.5°; pulse ranged between 120 and 140. Except for a rise in temperature to 102.8° on the evening of the twenty-third the course during the ensuing two weeks was one of steady improvement, with disappearance of all signs of pericarditis and pulmonary involvement, decline in tachycardia, decreasing leukocytosis, diminution in cardiac area, and normal or only very slightly elevated temperature. Drug withdrawal at the end of this period was uneventful. The patient entered then upon a prolonged subfebrile course, free from acute episodes.

CASE 19.—W. F., male, aged forty-one years, admitted February 20, 1929, on the twenty-fourth day of the first attack of rheumatic fever; temperature 100.6° , pulse 90, severe polyarthritis, congested fauces and pharynx, short systolic murmur at the base to left and right of the sternum, soft, diastolic murmur in 2d, 3d and 4th left interspaces; blood pressure 115 systolic, 40 diastolic; white blood cells 17,400. During the next forty-eight hours the temperature rose to 103.8° and there was spreading arthritis. February 22 at 11.30 A.M. he was given intramuscularly 20 cc. of V110A unconcentrated bovine serum without demonstrable effect on fever or pulse. February 23 at 8 A.M. temperature was 101.8° , pulse 88; the arthritis had ceased to spread but was more severe in the right hand; 20 cc. of serum at 11.30 A.M. During the day the temperature rose to 103.8° , the pulse to 100. February 24, the temperature was 100.8° , pulse 90. Most of the previously involved joints were improved; on the other hand, a few were worse and there was reinvolvement of joints which had been free for some time. During the day the temperature rose rapidly to 103.6° , to fall sharply during the night. February 25, there was considerable improvement, except for the newly involved joints of the day before, in which the process was at its height; February 26, these in turn had begun to yield and general improvement was quite marked. The temperature never became normal, however, and during the period February 27 to March 2 the febrile course was renewed; widespread and severe polyarthritis developed, and rapid loss of weight occurred. Neocinchophen therapy was instituted upon the latter day and a very prompt and gratifying improvement ensued. Except for a mild relapse attendant upon premature withdrawal of drug, the remainder of the patient's course was uneventful.

CASE 25.—N. S., male, aged forty-three years, admitted April 8, 1929, on the sixteenth day of his fifth attack of rheumatic fever; temperature 102.8° , pulse 92, moderately severe polyarthritis, chronic tonsillar infection, systolic murmur at apex poorly transmitted outward, systolic murmur in second left interspace, radial arteries slightly thickened, blood pressure 152 systolic, 85 diastolic. During a control period of ten days the disease was irregularly continuous, temperature 100.6° to 103.6° , pulse 90 to 100, arthritis never absent and at times very severe, steady loss of weight and strength. April 19, 3 cc. of concentrated scarlatinal antitoxin was given intramuscularly at 4.15 P.M. without immediate reaction. At 4 P.M. temperature was 101.6° ; at 6 P.M., 102° ; it declined steadily during the night. Similar declines had occurred nightly during the control period, so that the A.M. temperature of 100° was no lower than usual. The pulse hovered around 110° , about 6 points higher than usual. The morning of April 20 there was a severe exacerbation of the arthritis, with spreading to the hips and knees. At 10.45 A.M. 3 cc. of antitoxin was given. There was no reaction, and during the day the temperature failed to surpass 101° . April 21, arthritis considerably improved, and fever did not exceed 100.6° . The weight loss was checked. April 22, the relief was more pronounced; 4 cc. of the antitoxin was given at 2.30 P.M. without reaction; temperature not above 100° ; pulse range 110 to 120. Improvement continued for three days; there was then a five-day cycle of serum sickness with small-joint arthritis and urticaria. Following the spontaneous subsidence of this episode the further course was entirely satisfactory.

REFERENCES.

1. Levy, R. L., and Turner, K. B.: Variations in Auriculoventricular Conduction Time in Rheumatic Carditis with Salicylate Therapy, *Proc. Soc. Exp. Biol. and Med.*, 1927, 25, 64.

2. Small, J. C.: The Bacterium Causing Rheumatic Fever and a Preliminary Account of the Therapeutic Action of Its Specific Antiserum, *AM. J. MED. SCI.*, 1927, 173, 101; Rheumatic Fever: The Specificity of *Streptococcus Cardioarthritidis* in Rheumatic Fever and Sydenham's Chorea, *AM. J. MED. SCI.*, 1928, 175, 638; Rheumatic Fever: Present Development of the Biologic Products of *Streptococcus Cardioarthritidis*, *AM. J. MED. SCI.*, 1928, 175, 650.
3. Baruffaldi, T.: Serotherapy of Acute Articular Rheumatism, *Riforma med.*, 1926, 42, 1012.
4. Friedländer, M.: Ueber Rheumatismus, *Verhandl. d. deutsch. Kongr. f. inn. Med.*, 1885, 4, 403.
5. Menzer, A.: Serumbehandlung bei acutem und chronischem Gelenkrheumatismus, *Ztschr. f. klin. Med.*, 1902, 47, 109.
6. Schmidt, A.: Ueber die Behandlung des Gelenkrheumatismus mit Menzer'schem Antistreptokokkenserum, *Berl. klin. Wehnschr.*, 1903, 40, 1117.
7. Sinnhuber, F.: Die Behandlung des Gelenkrheumatismus mit Menzer's Antistreptokokkenserum, *Charité-Ann.*, 1904, 28, 128.
8. Menzer, A.: Die Reizbehandlung des akuten Gelenkrheumatismus, *Med. Klin.*, 1922, 18, 1022.
9. Toogood, E. S.: Scarlet Fever Antitoxin in a Case of Endocarditis and Myocarditis, *Lancet*, 1926, ii, 545.
10. Barach, J. H.: Acute Rheumatic Heart Disease Treated with *Streptococcus* Antitoxin (Scarlet Fever Serum), *J. Am. Med. Assn.*, 1927, 88, 1882.
11. Small, J. C.: The Rôle of *Streptococci* in the Rheumatic Diseases, *J. Lab. and Clin. Med.*, 1929, 14, 1144.
12. Reitter, C.: Der Anteil der Tuberkulose am akuten Gelenkrheumatismus, *Wien. klin. Wehnschr.*, 1928, 41, 473.
13. Swift, H. F.: Rheumatic Fever, *AM. J. MED. SCI.*, 1925, 170, 631.
14. Swift, H. F.: The Heart in Infection, *Am. Heart J.*, 1928, 3, 629.
15. Hill, N. G.: The Relation of *Streptococcus Cardioarthritidis* to Acute Rheumatism, Metropolitan Asylums Board Annual Report (London, England), 1928-1929, p. 385.
16. Wilson, M. G.: The Biologic Products of *Streptococcus Cardioarthritidis*, *J. Am. Med. Assn.*, 1930, 94, 842.

BLOOD TRANSFUSION IN THE ACUTE INFECTIOUS DISEASES.

AN ANALYSIS OF 100 CASES.

BY JOHN FITCH LONDON, M.D.,

CONSULTING PEDIATRICIAN (ASSISTANT), WOMAN'S HOSPITAL; ATTENDING PHYSICIAN, WILLARD PARKER HOSPITAL; ASSISTANT PEDIATRIST, ROOSEVELT HOSPITAL, NEW YORK CITY.

(From the Willard Parker Hospital.)

THE purpose of this article is to evaluate the transfusion of blood as a therapeutic agent in the treatment of the acute infectious diseases, their complications and sequelæ. One hundred cases in which transfusions were performed at the Willard Parker Hospital have been studied in an effort to attain more concrete knowledge as to the type of infectious diseases which is benefited by transfusion. The literature affords little information on this subject at present.

Both the direct (chiefly Lindeman) and the indirect methods of transfusion were employed. Without going into the controversy as to the relative efficacy of the two measures, it may be

stated that from our observation at the Willard Parker Hospital the direct method is the method of choice, provided members of the staff can be sufficiently trained to carry out the technique. The indirect method (citrate) is much employed and is in wide use at many excellent institutions, and, although admittedly attended more frequently by reactions of greater severity (in this series in the ratio of 5 to 1), it is simpler and should be the method of choice in a contagious disease hospital, if, due to the constantly changing nature of the staff, adequate instruction and experience in the direct method is not practical, or if the more complicated method interferes with carrying out the hospital aseptic technique, the purpose of which is the prevention of crossed infections.

The 100 cases studied cover a period of three and a half years, from January 1, 1926, when transfusions began to be regularly done, to May 1, 1929. Of the 100 cases analyzed, 35 died and 3 showed no improvement. During their stay in the hospital, the majority of these patients were, at one time or another, critically ill. In many instances, of course, transfusion was instituted to combat the complications rather than the primary disease. In the following tables, blood counts are not included because of the inadequacy of the records in this respect.

Diphtheria. Of 27 cases of diphtheria transfused, 15 died, a mortality of 55.5 per cent. (Cases No. 259 and No. 1948 had positive throat cultures, but not clinical diphtheria, and hence are not included.)

There were 9 cases of laryngeal diphtheria of which 2 (Cases No. 3140 and No. 2087), both uncomplicated, were transfused twenty-eight and twenty-seven days respectively after admission. Here the primary disease was already cured, the transfusion being employed as a tonic measure, and therefore these 2 cases are not included in computing the mortality for laryngeal diphtheria. Of the 7 remaining cases of laryngeal diphtheria, 4 died, a mortality of 57.1 per cent. Of these, 2 cases, Case 2949 complicated by empyema, Case 3118 complicated by bronchopneumonia, were reported as doing well until transfused, and died within twenty-four hours after the transfusion. Case 158, very toxic, died four days after transfusion, and Case 3006, complicated by bronchopneumonia, twelve days after transfusion.

Of the 3 cases improved or cured, in one, Case 2459, there was immediate improvement following transfusion and subsequent cure. No. 4559 complicated by bronchopneumonia, improved; and in Case 2371 the transfusion on two occasions was not completed because of very severe immediate reactions.

In short, in only 1 case of laryngeal diphtheria, Case 2459, can the transfusion be said to have been in any sense a life-saving measure. On the other hand, in 2 cases, death was probably hastened or precipitated by transfusion, while in the remaining cases no conclusion can fairly be drawn.

TABLE I.—DIPHTHERIA.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926.										
2459	10/13	M.	1 yr.	Laryngeal	10/16	I.	150	None	Cured	Respirations up to 70 before transfusion.
2820	12/13	M.	6 yrs.	Tonsillar; myocarditis	12/15	I.	210	None	Died	Myocarditis developed 2 days after transfusion; died 3 days after transfusion.
1927.										
170	1/20	F.	4½ yrs.	Tonsillar and pharyngeal	1/24	I.	200	None	Died	Died in 24 hours.
273	1/30	M.	19 mos.	Bilateral otitis media	2/4	I.	150	None	Cured	
2087	6/17	F.	17 mos.	Laryngeal	7/14	I.	200	None	Cured	Tonic.
2371	7/17	M.	1 yr.	Tonsillar and laryngeal; toxic	7/19	I.	125	Severe	Not improved	Very toxic.
					8/4	I.	75	Severe		Both stopped because of severe reactions.
2415	7/27	M.	1 yr.	Tonsillar and nasal	8/3	D.	200	None	Cured.	
2863	10/25	M.	4½ yrs.	Tonsillar; myocarditis	10/28	I.	180	Slight	Died.	
					10/29	I.	160	None.		
3006	11/15	F.	1 yr.	Laryngeal; bronchial pneumonia	11/18	I.	150	None	Died.	
3118	12/1	F.	2½ yrs.	Laryngeal; bronchial pneumonia	12/9	I.	None	Died	Doing well until transfusion; died in 24 hours.
3164	12/7	F.	12 yrs.	Toxic; heart block	12/9	I.	250	None	Died	Six days after transfusion developed heart block.
1928.										
55	1/7	F.	5½ yrs.	Nasal and tonsillar diphtheria	1/9	I.	200	None	Cured.	
541	2/11	M.	2 yrs.	Tonsillar diphtheria	2/29	D.	200	None	Cured.	
1031	3/9	F.	2 yrs.	Tonsillar; S.F.; erysipelas; bronchial pneumonia	3/30	D.		None		
					4/26	D.	240	None	Cured	Transfusion succeeded where S.F. antibacterial vaccine and erysipelas antitoxin failed.

2949	5/25	M.	2½ yrs.	Laryngeal diphtheria; empyema	6/21	D.	120	None	Died	Marked anemia.
3140	12/4	M.	3½ yrs.	Laryngeal and pharyngeal diphtheria	1/24	D.	100	None	Improved.	
4203	8/23	M.	7 mos.	Pharyngeal diphtheria; myocarditis; acute intestinal intoxication	8/24	?	200	None	Died 9/10	Probably died of intestinal intoxication.
4559	10/27	M.	2 yrs.	Streptococcic sore throat	10/17	D.	260	None	Cured.	
1929.										
158	1/10	M.	27 yrs.	Laryngeal diphtheria; bronchial pneumonia	1/12	D.	300	None	Died in 4 days	Tracheotomy.
259	1/15	F.	3 yrs.	Diphtheria by culture; rickets; pulmonary tuberculosis	1/21	D.	320	None	Cured	Very anemic.
1007	3/6	F.	2 yrs.	Nasal; cervical adenitis; streptococcus septicaemia	3/11	D.	260	None	Died 3/11	
1321	3/22	F.	25 yrs.	Toxic diphtheria, pharyngeal; myocarditis	3/23	D.	500	None	Died 3/24	Myocarditis before transfusion.
1452	3/28	F.	8 yrs.	Nasal and tonsillar diphtheria, toxic; multiple neuritis; rheumatic heart disease; myocarditis	3/30	D.	400	None	Not improved	Taken home against advice; persistent nasal bleeding; myocarditis developed.
1510	3/31	F.	4½ yrs.	Tonsillar and laryngeal; acute streptococcic sore throat; bronchial pneumonia	5/9	D.	200	None	Died	Died within 24 hours of transfusion; died of streptococcic throat.
1543	4/1	F.	2½ yrs.	Nasal; myocarditis	4/2	D.	200	None	Died 4/2	Persistent nasal bleeding.
1642	4/6	M.	2 yrs.	Tonsillar diphtheria; bronchial pneumonia; right otitis media	4/19	D.	200	None	Cured	Transfusion brought temperature to normal.
1669	4/8	F.	20 yrs.	Tonsillar and palatal diphtheria, toxic	4/12	D.	200	None	Cured	
1948	4/24	M.	10 mos.	Diphtheria by culture; otitis media; mastoiditis	5/11	D.	220	None	Cured	Reinfection of old mastoid, not operated.
5167	12/29	M.	4 yrs.	Toxic diphtheria; mastoiditis; myocarditis	1/31	D.	200	None	Died 2/2	Throat filled with mucus at time of transfusion; very toxic.

NOTE.—Improvement means that the case left the hospital either at the patient's own risk, or was transferred to a general hospital before a cure was effected. Practically without exception these cases were out of danger when released or transferred.

TABLE II.—SCARLET FEVER.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926. 2398	9/28	F.	2½ yrs.	Tuberculous glands with sinus	10/18	I.	250	None	Improved	Dehydration, anemia.
1927. 91	1/13	F.	2½ yrs.	Empyema	1/24	I.	165	None	Much improved.	Died within 24 hours.
353	2/9	F.	6 yrs.	Cervical adenitis; mastoidectomy	2/11	I.	200	None	Died	
1140	4/4	F.	2 yrs.	Otitis media, empyema	4/7	I.	150	None	Cured.	
1184	4/7	F.	3 yrs.	Otitis media, empyema	4/23	I.	150	Moderate	Cured.	
1388	4/20	F.	2½ yrs.	Foreign body in bronchus; otitis media; serum rash	4/26	I.	125	Slight	Much improved.	Home on release.
2527	8/18	F.	12 mos.	Diphtheria	8/28	I.	250	Slight	Improved	
1928. 620	2/16	F.	2 yrs.	Otitis media; nephritis	3/14 3/19	D. D.	140 150	None None.	Cured.	
1663	3/8	F.	9 yrs.	Bronchial pneumonia; empyema	3/25	D.	None	Cured.	Very toxic; no improvement.
1811	4/9	F.	25 yrs.	Bronchial pneumonia; bronchial empyema	4/15	D.	500	None	Died 4/17	Moderate anemia.
2463	5/5	M.	2½ yrs.	Dementia precoc; pneumonia	5/28	...	250	Cured	Moderate anemia, hemoglobin 60 per cent; red blood cells, 2,300,000.
3071	11/23	F.	3 yrs.	Mastoidectomy	11/27 11/29	I. I.	220 160	None None	Cured	

3150	6/1	M.	4 yrs.	Empyema and multiple abscesses; otitis media; nasal diphtheria.	6/21 ..	D. D.	250 200	None	Improved	Home on release.
3345	12/30	F.	6	Mastoiditis	1/3	I.	100	Moderate	Cured	1/26/29, hemoglobin 70 per cent; red blood cells, 4,640,000.
3532	4/19	F.	15 mos.	Bronchial pneumonia, catarrhal laryngitis; septicemia	6/29	D.	225	Marked	Died.	
4418	10/7	F.	30	Acute mastoiditis; otitis media	10/18	I.	200	None	Cured	Transfusion stopped because of clot.
4624	11/6	F.	10	Otitis media; cervical adenitis	12/1	D.	300	None	Cured.	
4707	11/14	M.	7	Double mastoiditis	11/15 11/22	D. D.	300 280	None	Cured.	
1929. 1160	3/14	M.	5	Septicemia	3/16 2/27	D. D.	320 180	None	Died 3/16	Acute septic.
1261	3/9	M.	6	Lobar pneumonia	3/20	D.	120	None	Died	Admitted on twenty-third day of illness; developed pneumonia 10 days after transfusion.
1282	3/20	F.	28	Sepsis; bronchial pneumonia; pleurisy; lung abscess	4/22	D.	550	None	Died 4/25	
1530	4/1	M.	3½	Lobar pneumonia; empyema and gangrene of lung	4/20	D.	320	None	Died	Very toxic.
1563	4/2	F.	2	Bronchial pneumonia; bacteremia	4/4	D.	230	None	Died	No improvement.
1891	4/21	F.	15	Toxic scarlet fever	4/24	D.	470	None	Died 4/25	Given too much blood.
5185	12/29	M.	14	Mastoiditis; right sinus thrombosis	2/1	I. I.	476 500	None None.	Cured	

TABLE III.—MEASLES.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926.	4/27	M.	2½ yrs.	Scarlet fever; otitis media; bronchial pneumonia	5/19	D.	150	None	Cured.	
1355	5/3	M.	11 mos.	Bilateral otitis media; bronchial pneumonia	5/26	D.	150	None	Cured	Mastoidectomy 6/22; anemia marked; had pneumonia on admission.
1654	5/27	F.	6 yrs.	Acute appendicitis, operated	6/1	I.	120	None	Improved	Vomited ascaris lumbricoides following operation.
1663	5/28	F.	9 mos.	Bronchial pneumonia; bilateral otitis media	6/4 6/7	I. I.	75 50	None	Died 6/9	
1710	6/1	M.	3 yrs.	Otitis media; bronchial pneumonia; pyelitis	6/24	I.	172	None	Cured	Anemia.
2496	9/20	F.	2 yrs.	Pertussis; left conjunctivitis; bronchial pneumonia	10/27	I.	180	None	Improved.	
1927.	9/13	F.	9 yrs.	Bronchial pneumonia	6/4	I.	100	None	Died.	
1722	5/17	F.	2 yrs.	Bronchial pneumonia; otitis media	6/8	I.	65	None	Much improved	Saved life.
1765	5/19	M.	6 mos.	Otitis media; bronchial pneumonia; empyema; mastoiditis	6/11 6/22	I. I.	110 115	None Marked	Much improved	Home on release; temperature normal.
1866	5/17	M.	11 mos.	Otitis media; mastoiditis; bronchial pneumonia	5/30 7/14	I. I.	50 150	None Slight	Cured	No operation.
1928.	1/16	F.	1 yr.	Bronchial pneumonia; otitis media	2/3	I.	85	None	Cured.	
1565	3/20	F.	3 yrs.	Mastoiditis; arthritis, left knee	4/30 5/6	D. D.	200 160	None None	Cured Improved	Tonic.
2403	5/2	M.	1½ yrs.	Cervical adenitis	5/16	D.	180	None	Improved	Cured.
3210	6/3	F.	2 yrs.	Bronchial pneumonia; otitis media	7/19	I.	205	None	Improved	Cured.
3632	6/26	M.	11 mos.	Otitis media; bronchial pneumonia	7/31	I.	220	Improved	Improved	Discharged on release.
3647	6/27	M.	16 mos.	Bronchial pneumonia	7/22	D.	220	None	Improved.	
3677	6/29	F.	6 yrs.	Cerebrospinal meningitis	7/7	D.	350	None	Died.	
4031	2/2	M.	7 yrs.	Pneumonia; otitis media	2/15	I.	180	None	Cured.	
2249	6/2	Uncomplicated	6/29	I.	300	None	Cured	Tonic.

TABLE IV.—PERTUSSIS.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926.										
2227	8/16	M.	4 mos.	Gastroenteritis Bronchopneumonia	9/13	I.	75	None	Cured Cured	Dehydration; anemia. Followed by crisis.
2520	10/28	M.	2½ yrs.		19/19	I.	160			
1927.										
2652	9/14	M.	18 mos.	Bronchopneumonia	9/23	...	100	Severe Slight Slight Died Improved	Transfusion stopped because of collapse. No convulsion after transfusion; temperature 106.6° at one time, plus convulsions.
2662	9/15	M.	14 mos.	Bronchial pneumonia; rickets; convulsions	9/28 9/17	I. I.	150 150			
2808	10/17	M.	1 yr.	Gastroenteritis; dehydration Bronchial pneumonia Bronchial pneumonia; otitis media	10/20	I.	125	Slight None Moderate	Cured. Cured. Cured.	
2841	10/22	F.	3 yrs.		10/27	I.	200			
2880	10/27	F.	14 mos.		11/6	I.	200			
2960	11/8	M.	6½ mos.	Stomatitis; acute otitis media; bronchial pneumonia	11/15	I.	180	Moderate	Cured.	
3068	11/23	F.	2½ yrs.	Bronchial pneumonia; malnutrition	12/6	I.	40	None	Cured.	

TABLE V.—MISCELLANEOUS.

Hosp. No.	Date of admission.	Sex.	Age.	Complications.	Transfusion.			Reaction.	Results.	Remarks.
					Date.	Method.	Amount.			
1926.	11/9	F.	2½	Foreign body, left bronchus	11/10	I.	50	None	Died	Chestnut shell in bronchus.
2599	6/1	F.	13 mos.	Streptococic septicemia; bronchial pneumonia	6/8	I.	80	None	Died.	
1918	7/2	F.	55	Streptococic septicemia	7/6	I.	500	None	Improved	Erysipelas.
2240	8/2	F.	4	Poliomyelitis (bulbar)	7/12	I.	500	Slight	Not improved	Home on release; intraperitoneal used; intravenous failure.
2441	8/5	M.	8	Poliomyelitis and respiratory paralysis	..	I.	150	None	Died	
2456	8/5	M.	6	Postmeasles encephalitis	8/13	I.	225	None	Improved	
2493	5/6	M.	5	Typhoid fever; bronchial pneumonia	5/7	D.	400	None	Died	In coma when transfused; died 4 hours after second.
2627	9/15	M.	14	Typhoid fever	5/9	D.	300	None	Cured.	
2058	9/14	M.	14	Retropharyngeal abscess (bilateral); rickets	9/13	I.	200	Marked	Cured.	
2678	10/5	F.	14 mos.	Abscess, right buttock; rickets; malnutrition; naso-pharyngitis	10/7	I.	180	None	Cured	Blood culture, Gram-positive diplococci.
2761	11/10	F.	20 mos.	Lobar pneumonia; otitis media	10/8	D.	200	None	Improved	Hematuria.
2967	1/19	F.	2½	Streptococic throat; meningitis; bronchial pneumonia	9 21	I.	150	Slight	Cured.	
1928.	2/2	M.	10½	Poliomyelitis (bulbar)	11/14	I.	100	Moderate	Cured.	
400	5/13	F.	35	Acute sinusitis; otitis media; mastoiditis; lateral sinus thrombosis; septicemia and meningitis	1/25	I.	200	Died.	Critically ill; died 2 hours after transfusion.
2669	10/17	M.	2	Streptococic sore throat	2/7	D.	350	None	Died	Moribund when transfused.
4488	1/24	F.	18 mos.	Cellulitis	6/8	D.	500	None	Cured.	
1929.	1/31	F.	18 mos.	Varicella; bronchial pneumonia; cellulitis, chest wall	6/15	D.	500	None	Improved	Transferred to Bellevue.
519	2/24	F.	5 mos.	Varicella; gastroenteritis; otitis media	2/3	D.	160	None	Died	Died 3 days after transfusion.
864					2/1	D.	200	None	Improved	Transferred to Bellevue.
					3/1	D.	100	None	Improved	

Of the 27 cases of diphtheria transfused, there were 8 cases designated as toxic. Of these, 4 died, another probably died outside the hospital, 2 were cured, and 1 improved.

From experimental work on cats and rabbits, Harding¹ has concluded that transfusion may be of some value in the toxic stage of diphtheria. However, the results just quoted hardly bear out this theory.

Seven cases in which myocarditis was present or developed, were transfused. Of these, 6 died, and 1 was released against the advice of the hospital in a moribund condition. Three died within twenty-four hours after transfusion. Two cases developed myocarditis after transfusion, three to six days respectively, the remainder having had evidences of myocarditis before transfusion.

In short, transfusion neither was of aid in preventing injury to the myocardium nor successful in saving the lives of those patients in whom myocarditis was present, so it appears that transfusion is absolutely contraindicated in diphtheria complicated by myocarditis, simply throwing an unnecessary burden on the weakened heart muscle, and of no value and probably harmful in laryngeal diphtheria, especially at the height of the disease or when bronchopneumonia is present. Transfusion appears to be of benefit in protracted cases in which malnutrition or anemia develops (Cases 2087 and 3140).

Scarlet Fever. Of 25 cases of scarlet fever that were transfused, 9 died, a mortality of 36 per cent. Of the 9 deaths, 3 cases died of the uncomplicated primary disease. Transfusions had no effect whatever on the course of these acute toxic scarlatinas, 2 dying within twenty-four hours and the third three days after transfusion.

Of the remaining 6 cases which died one was complicated by lobar pneumonia, empyema and gangrene of the lung. There were 3 deaths from bronchopneumonia, but 2 of these cases were complicated by septicemia and bacteremia and the third was a very toxic case which would probably have succumbed anyway. In this connection, Stetson² has reported 10 recoveries in 19 transfused cases of *Streptococcus hemolyticus* bacteremia. Warren and Herrick,³ on the other hand, report only 10 recoveries in 31 cases which were not transfused.

Of the 16 cases which were improved or cured, there were 2 cases complicated by empyema, 2 cases complicated by bronchopneumonia and empyema, 3 cases of cervical adenitis, 7 cases of mastoiditis, of which one had a sinus thrombosis. There were no deaths from mastoiditis in the transfused cases. Both in preparing patients for mastoidectomy and as an adjuvant in convalescence, transfusion seems to have won a well-merited place. In Case 5185, complicated by sinus thrombosis, which was seen by the writer, there was little doubt but that the transfusion was life-saving.

Feinblatt⁴ also has had excellent results with transfusions in cases of sinus thrombosis.

Its use also seems justified in the pre- and postoperative cases of empyemas. Of the 2 cases listed which died, one was moribund when transfused and the other developed gangrene of the lung.

Again, as a general tonic late in convalescence when the patient has become badly malnourished or anemic, or in the more protracted types of complications such as cervical adenitis or nephritis, transfusion appears to be of use. Its value against bronchopneumonia cannot be judged because of the complicated nature of the cases studied in this group.

Measles. Of 19 cases of measles transfused, 3 died, a mortality of 15.8 per cent. Of the 3 deaths, Case 1722, complicated by bronchopneumonia, died twenty-four hours after admission, Case 1663, complicated by bronchopneumonia and otitis media, died two days after the last of two transfusions, and Case 3677 developed cerebrospinal meningitis. Of the 15 cases which improved or recovered, 9 complicated by bronchopneumonia were transfused seven to forty-six days after admission, the average being twenty-five days. Two cases complicated by empyema and 3 by mastoiditis were improved or cured.

Transfusion in measles appears to be of definite value in the cases complicated by bronchopneumonia. The results also justify its use in empyema and mastoiditis.

NOTE.—This mode of treatment should not be confused with the intramuscular injection of convalescent serum or whole blood, which was extensively tried out by Zingher⁵ at this institution several years ago.

Pertussis. Of the 9 cases of pertussis transfused, one died, a mortality of 11.1 per cent. The one death, Case 2652, may probably be attributed directly to the transfusion, as the patient went into collapse while being transfused.

The 7 cases which improved or were cured, were transfused on the second to the twenty-fourth day after admission, the average being twelve days. Five of these cases were complicated by bronchopneumonia and 2 by gastroenteritis. In general, it may be said that the bronchopneumonias reacted well to transfusion, there being but one death in 6 such complicated cases, but that it is not unattended by danger is shown by the collapse in the instance of Case 2652.

Miscellaneous. Three cases of the bulbar type of poliomyelitis were transfused, with 100 per cent mortality. Three cases of varicella in infants were transfused, of which one died three days after transfusion, 2 were improved and transferred to Bellevue Hospital. There were 2 cases of typhoid fever, both of which were cured. Ottenberg and Libman,⁶ on the other hand, report recovery of only 2 out of 9 patients critically ill with typhoid. Two cases of strepto-

coccus septicemia were transfused with one recovery. One post-measles encephalitis died four hours after transfusion.

Summary. 1. Blood transfusion appears to be contraindicated in diphtheria complicated by myocarditis, and in laryngeal diphtheria particularly when bronchopneumonia is present.

2. It is a valuable adjuvant in the pre- and postoperative care of mastoiditis, sinus thrombosis and empyema, particularly when these conditions are complications of scarlet fever or measles.

3. It is of value in the treatment of bronchopneumonia complicating measles and pertussis.

4. As a general tonic in protracted cases in which anemia and malnutrition develop its use is strongly indicated.

BIBLIOGRAPHY.

1. Harding, M. E.: The Toxemic Stage of Diphtheria, With Special References to Pathology and Treatment, *Lancet*, 1921, i, 737.
2. Stetson, R. E.: The Therapeutic Value of Blood Transfusion With Report of 68 Cases of Sepsis, *AM. J. MED. SCI.*, 1924, 168, 534.
3. Warren, W., and Herrick, N. W.: Analysis of 134 Cases of Bacteremia, *AM. J. MED. SCI.*, 1916, 151, 556.
4. Feinblatt, H. M.: Transfusion of Blood, Macmillan, 1926, p. 69.
5. Zingher, A.: Convalescent Whole Blood, Plasma and Serum in Prophylaxis of Measles, *J. Am. Med. Assn.*, 1924, 82, 1180.
6. Ottenberg, R., and Libman, E.: Blood Transfusion; Indications; Results General Management; *AM. J. MED. SCI.*, 1915, 150, 36.

ON SOME VENOUS MURMURS FOUND IN HEPATIC CIRRHOSIS AND THEIR CONFUSION WITH MURMURS OF CONGENITAL HEART DISEASE.

BY NORMAN B. GWYN, M.D.,

TORONTO.

ONLY some detail of special interest can justify further discussion upon the nature of venous murmurs; well recognized since the time of Laennec and Bouillaud, described as occurring under many and different circumstances, and in so many of the hidden corners of the body, we have come to look upon them as mere matters of passing interest. Placed in certain situations, however, a venous murmur has been known to create some difficulty in diagnosis, as is evidenced by the description of Palmer and White¹ of the sounds which may be produced in the innominate and superior caval veins by the flow from the internal and external jugulars. The fact, stressed in their description, that some of the loud continuous murmurs heard over the upper sternum and down about the second and third right intercostal spaces can be obliterated by pressure upon the external jugular, does not seem to be a matter of general

recognition, and those interested in venous murmurs which may be so placed as to suggest some congenital affection of the heart should consult the excellent résumé given by these writers.

Palmer and White bring the venous murmurs arising from the confluence of the jugulars, the subclavians and the innominates down to the upper heart limits, while Thayer,² working from below, so to speak, brings the venous hums of the abdomen, those so often recorded in association with cirrhosis, up to the lower heart borders, including in his discussion the description of one murmur, presumably of venous origin, which could be followed from the xiphoid area to the episternal notch. This particular instance of a venous murmur developing over the heart area in the course of a hepatic cirrhosis, another recorded by Fell³ subsequent to a wound of the sternum and those of my own would seem on the one hand to bridge the gap as concerns the placing of a venous hum directly over the heart area, and on the other to excuse the somewhat incomprehensible title of this contribution.

As has been indicated, I am not attempting in this short report to discuss the causes of venous murmurs, but wish to describe the conditions which existed in 2 rather remarkable cases which had been considered cases of congenital heart disease, until it was shown that the confusing murmur could be completely removed by the simple process of laying a finger upon the spot over the heart area, under which a hidden vein was coursing.

Murmurs developing in association with the varicosities which we know to exist when cirrhosis of the liver has progressed to a certain degree are not uncommon.⁴ They usually belong, however, to the region of the ensiform cartilage or the subdiaphragmatic areas, and have been readily explained when once the existence of cirrhosis with its venous dilatations has been recognized. In some few instances dissection has shown an arrangement of venous channels,⁵ which seemed to be such that it could explain the remarkable murmurs heard while circulation was going on; it might be difficult, however, to fix a murmur heard during life upon any arrangement of empty nonfunctioning vessels disclosed by examination after death. In the cases to be detailed a simple procedure seemed to throw much light on the "point of origin" at least of two oddly placed venous murmurs, while the fact, that in both instances the diagnosis of congenital heart disease could be absolutely excluded by the same simple procedure, seems not without some degree of interest.

Beginning with a description of the second case, who is still alive, it will be enough to say that he was presented at a clinic gathering as a case of congenital heart disease, because of the loud roaring continuous murmur heard over the base of the heart and toward the foot of the sternum. The murmur suggested by its qualities, position and disposition the existence of some gross defect

in the cardiac septa, and those interested in the presentation of the case inclined to the idea of a defect in the interventricular septum. Other possibilities connected with the heart were naturally considered, and a striking coincidence was a systolic murmur about and to the left of the abdominal aorta in its lower part. The patient gave a history of alcoholism, his spleen was much enlarged and his liver was easily felt. Further details of the case are that there is no cyanosis and no clubbing of the fingers. The absence of these physical signs, however, by no means rules out the possibility of congenital heart lesion, and there was certainly the tendency to associate the much-enlarged spleen and the large liver with a degree of chronic passive congestion, although there was no sign of edema in the lungs, abdomen or extremities. The murmur as charted seemed best heard just to the left of the midsternum at the level of the fourth interspace. It was loud roaring and with a systolic intensification; it was associated with a distinct thrill, and was transmitted a considerable distance in all directions, but not particularly into the vessels of the neck or to the pulmonary artery district. It could be heard in the back, and seems to conform to the description of murmurs which result from defects in the auricular or ventricular septum. All the questions, however, as to the point of origin of the murmur, and its meaning, seemed to be answered by the fact that the lightest possible pressure at the point indicated in the picture Fig. 1, causes the murmur to disappear at once. This, of course, tells one that it has nothing to do with a heart condition and promotes at once further investigation.

Palpation of the sternum discloses a slitlike fissure just to the left of the midline, and one sees that the point at which a gentle pressure will obliterate the murmur is immediately above this fissure. The probability is that a vein is discharging through this fissure to pour into larger venous channels beneath and is meeting other currents in such manner that a murmur is produced. The history of alcoholism, the large liver, the large spleen suggest at once the existence of hepatic cirrhosis or portal thrombosis, and one surmises that in this case we are dealing with one of the curious anomalies which at times may be met with in the development of a collateral circulation, an anomaly doubly interesting from the fact that its point of discovery is placed high enough to cause confusion with certain murmurs which are held to suggest congenital heart disease.

The suggestion that pressure about this or that area might influence the murmur followed naturally from experience in connection with other venous hums. In the following out of one we found that slight pressure upon the external jugular vein caused the disappearance of a loud roaring murmur heard in the first and second right interspaces, over the right heart border and behind the right

shoulder.⁶ In the consideration of another, one which imitated closely in quality and distribution the murmur already described, and which in turn had suggested congenital heart disease, we were able to see the structural conditions, which at least contributed to the auscultatory findings.

In the AMERICAN JOURNAL OF THE MEDICAL SCIENCES (1912, 143, 72) is described a case which I had the pleasure of dissecting for Dr. J. Norman Henry, of Philadelphia. We had watched the patient for many months, interested in a loud roar at the lower

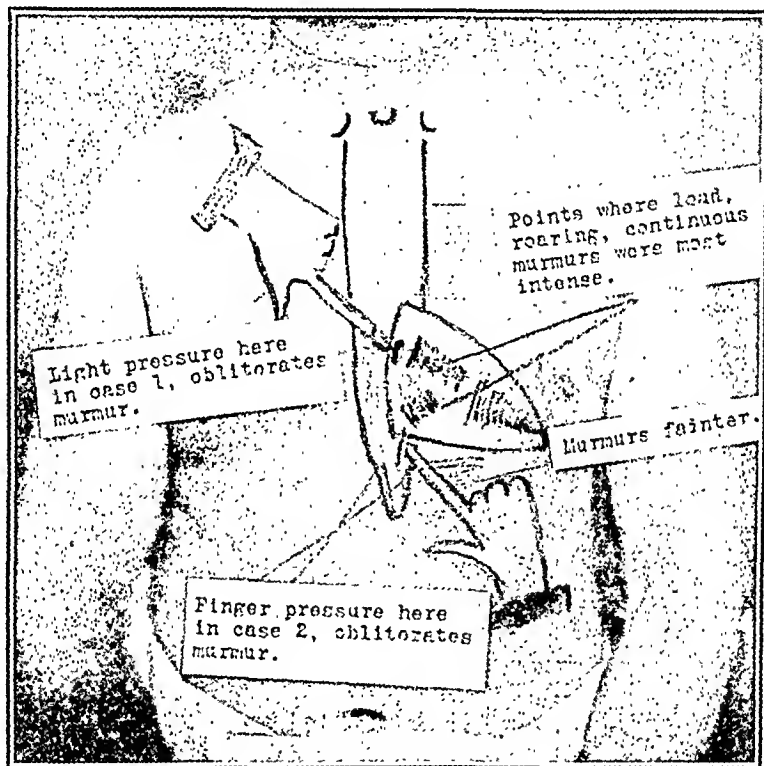


FIG. 1.—Diagrammatic sketch, showing the situation of fissures in the sternum and points at which the murmurs were best heard in the two cases reported. These fissures which result from some disturbance of the proper process of ossification in the sternal segments are very common. A developing collateral circulation in the course of cirrhosis would be very likely to find a way through any such deficiency.

sternal area, continuous, heard over the precordium and showing slight intensification both with inspiration and with the heart systole. We had in our turn made the mistake of inclining to the idea that this murmur represented congenital heart disease rather than a hum produced in the veins. The position of the murmur, well above the xiphoid, and its systolic intensification were the points which influenced us most. The diagnosis for many weeks remained "case of defect of interventricular septum." Quite by accident we discovered that slight pressure of the finger at the

point indicated (Case I) Fig. 1, completely obliterated the murmur, although at this time there was little if any sign of venous dilatation or obstruction. As the months went on the picture of cirrhosis of the liver was faithfully reproduced: the liver enlarged, the spleen projected from below the costal margin and veins could be seen coursing upward to the epigastric and sternal areas as well as downward to the groin. Pressure on one particular vein could be shown to regularly obliterate the murmur. As in the case described in the same year by Dr. W. S. Thayer,² this murmur disappeared of itself a few hours before death.

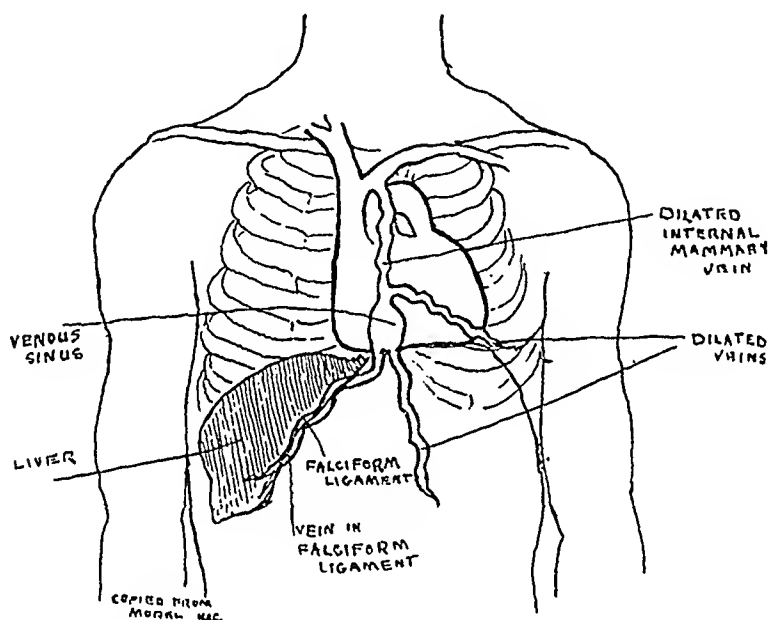


FIG. 2.—Diagrammatic representation of conditions which may be present in some instances of well-developed collateral circulation and of the condition found in Case II. The liver and falciform ligament are indicated as is the vein coming from the ligament through the diaphragm. The venous sinus is roughly represented as lying over the lower part of the right ventricle. The venous trunk, the enlarged internal mammary leading from it up over the heart and joining with the innominate vein is seen to pass directly over the heart area. The production of a murmur directly over the heart would be explained by the existence of this abnormality in the venous circulation, particularly if into this sinus was emptying a vein which coursed through the sternum.

Dissection gave one an idea at least as to the method of production of the murmur and also seemed to explain why it could be heard up toward the heart area. The well-known lesions of cirrhosis of the liver were in evidence, and there were many dilated veins in various parts of the body. The vein which contributed most to the murmur seemed to run up to the sternum and perforated a small fissure at the xiphosternal junction. Immediately beneath the sternum and xiphoid this vein could be seen to enter a large venous sinus, about 4 by 4 cm., situated in areolar tissue just under the

bone. Into the sinus, and coming directly through the diaphragm, ran another large vein, and this vein in turn could be seen to come from the suspensory ligament and to be connected with the moderately distended umbilical veins. From the upper part of this sinus there was wide open venous connection with the much dilated left internal mammary vein, and as it is highly probable that the blood current would be directed upward toward the left innominate vein and the superior cava, the murmur would tend to be transmitted over the heart and toward the great vessels. One cannot say, of course, in just what part of these venous channels the murmur would be produced: the probability is, however, that it would be where the vein entered the large sinus, for here would be the meeting of the blood currents and the general conditions which seem necessary for the production of venous sounds. With a dilatation of the trunk of the left internal mammary vein as it courses upward to penetrate the superior mediastinum on its way to the innominate, there would be opportunities for sound transmission directly over the right ventricle and auricle. One feels that in the case reported by Gambarati⁷ the ability to follow the murmur upward to the episternal notch depended upon some such arrangement of venous channels. The diastole of the heart might compress these overgrown venous structures to such a degree that a diastolic lessening of sound would take place; with the heart's systole such an assumed partial obstruction might be removed. One thing would seem certain: Upon the left internal mammary vein would depend the collateral circulation of that part of the body wall directly over the pericardium.

Fig. 2 attempts to illustrate what existed in Gambarati's case and in the case of my own dissection; it probably represents more or less accurately what exists beneath the sternum and over the heart in the second case I have detailed and shows that a combination of a very common anomaly with a very usual development may quite easily give rise to confusing physical signs.

Summary. 1. Clefts in the sternum due to some defect in the process of ossification constitute a not uncommon anomaly.

2. The collateral circulation which develops in the course of cirrhosis of the liver may easily provide venous trunks which may pass through such clefts enroute to sinuses of considerable size beneath the sternum.

3. A loud murmur may be produced by the fluid eddies which will be present in such vascular connections.

4. Such murmurs, if continuous and found in the neighborhood of the third, fourth or fifth interspaces of the left side, may well be confused with those of congenital heart disease.

5. Before coming to any conclusion in connection with continuous murmurs over the heart area, finger pressure should be carefully applied to areas immediately adjacent to the sternum.

NOTE.—Hope, in his work, "A Treatise on the Diseases of the Heart and Great Vessels and on the Affections Which May be Mistaken for Them," 1832, gives, perhaps, the best description of venous murmurs, particularly those heard in the neck. Landis (Arch. Pediat., 1912, 29, 88) gives an excellent description of these murmurs. He details well the Eustace-Smith murmur and gives as well an excellent bibliography. Blake (Clin. J., London, 1911–1912, 39 and 40, 146 and 239) describes murmurs in congenital heart disease very like those in Cases I and II described above.

REFERENCES.

1. Palmer and White: New England J. Med., 1929, 199, 1297.
2. Thayer: AM. J. MED. SCI., 1911, 141, 313.
3. Fell: Jour. Am. Med. Assn., 1919, 72, 1669.
4. Rolleston: Diseases of the Liver and Bile Duets. Thayer (*vide supra*).
Von Jaksch. Taylor: Guy's Hosp. Repts., 1895. Gambarati: Riforma méd., 1903, 19, 153.
5. Piazza-Martini, quoted by Thayer. Piccini, quoted by Thayer. Braune, quoted by Thayer.
6. See the descriptions given by Palmer and White (*vide supra*).
7. Gambarati, quoted by Thayer (*vide supra*).

OBSERVATIONS UPON CHRONIC CHOLECYSTITIS.

WITH SPECIAL REFERENCE TO MOTOR DISTURBANCES OF THE
GASTROINTESTINAL TRACT IN RELATION TO PREOPERATIVE
AND POSTOPERATIVE SYMPTOMS.

BY NOBLE W. JONES,

PROFESSOR OF CLINICAL MEDICINE, UNIVERSITY OF OREGON MEDICAL SCHOOL,
AND

DORWIN L. PALMER,

CLINICAL PROFESSOR OF RADIOLOGY, UNIVERSITY OF OREGON MEDICAL SCHOOL.

WITH CHEMICAL STUDIES BY R. B. ADAMS.

(From the Department of Medicine, University of Oregon Medical School.)

IN this paper are reported the results of a study of chronic cholecystitis with special reference to the roentgenologic technique employed and to certain factors which influence diagnosis, which cause in large measure the clinical symptoms of the disease, and which also cause the continuance of these symptoms after operation. The study is based upon an analysis of 482 cases which were diagnosed chronic cholecystitis and operated upon for this disease, and upon an end-result analysis of 666 postoperative cases. The cases in the first group are included in the cases of the second group. Neither group includes cases of acute suppurative cholecystitis nor carcinoma of the bile tract. As an attempt to correlate better the roentgenologic factors of diagnosis, chemical studies of normal and diseased gall bladders and their bile content are also reported.

Part I. The Method. The examination of the gall bladder by the older methods, in our opinion, deserves more attention than is now given to it. The history of the development of roentgenologic methods of examining the gall bladder dates from the early nineties, but it was not until 1922 that George and Leonard¹ published a procedure for the satisfactory demonstration upon plates of the diseased gall bladder. Although their work was repeated and verified in other laboratories, many investigators failed to duplicate their results. The publication of their technique brought forth no new principles; the authors merely listed the technical steps which had brought them success.

The studies herein related have for their object: (1) To investigate the truth of the assertion made by these authors that only a diseased gall bladder will produce a shadow upon the direct film; (2) to correlate the state of the gall bladder which may give such shadow upon the film and the spasm and distortion of the gastrointestinal tract; and (3) to determine, if possible, how far this correlation may aid in the recognition and differentiation of chronic gall bladder diseases. These studies, conducted over a period of several years, have led us to certain opinions and conclusions.

In order to obtain satisfactory direct films by the method of George and Leonard we find it necessary to follow rigidly certain technical details. The patient must be properly prepared by having his colon cleansed and freed of gas, if possible. For this latter purpose enemas have been found more satisfactory than cathartics, which tend to increase rather than diminish the quantity of gas present in the colon. Before films are made the patient is observed fluoroscopically and, if the colon contains sufficient gas to interfere with satisfactory films, an attempt is made to eliminate it by means of further enemas. This method of preparation is not always successful, however, for there are persons who do not tolerate enemas without resultant distention. When a satisfactory preparation by the use of enemas seems to be impossible the patient is placed for several days upon a smooth regulatory diet and is given antispasmodics. When he is ready for examination he is carefully instructed how to hold his breath and relax his muscles. This step is important, for the slightest movement of the patient will obliterate soft tissue detail. One film is then made, developed and read. Any necessary change in technique is then decided upon, for the technique must be adapted to the patient's body characteristics. In this manner six to eight films are taken, but even with this painstaking procedure satisfactory films are not always obtained.

When properly carried out, however, the above technique usually produces films that have a wealth of soft tissue detail. Indeed, this detail is sometimes confusing. One may sometimes note, in addition to the sharp margin of the liver and kidney, a number of shadows having the same size, location and contour as the shadow

of the gall bladder. Such shadows are cast, as Case 2 has emphasized, by the gastric antrum, the duodenum, the colon and other neighboring structures. However, it is easy to identify the gall bladder shadow by comparing the direct films with those taken after the oral administration of tetraiodophenolphthalein. The necessity for this comparison, however, occurs in only a small percentage of patients.

The administration of tetraiodophenolphthalein when used alone as a diagnostic procedure has, in our experience, distinct limitations. It shows obstruction of the cystic duct, either partial or complete; it frequently shows the outline of cholesterol stones; it shows distortions and irregularities of the gall bladder contour. It does not, however, reveal disease of the gall bladder wall, and its use, in consequence, may be unnecessary except when the direct films are unsatisfactory or show multiple shadows.

A factor overlooked when the method of Leonard and George is discarded is that alteration in the chemistry of the gall bladder wall, and possibly the bile content, occurs with disease, and that this chemical change may have something to do with the production of shadows on the direct Roentgen ray films. When one bases roentgenologic opinion on the Graham-Cole test alone the evidence of disease, as influenced by altered inherent chemistry, is lacking. Although the use of tetrabromphenolphthalein, and later of tetraiodophenolphthalein, has been, undoubtedly, a great aid in diagnosis, the universal employment of these dyes has distorted roentgenologic opinions. According to our observations, too much reliance is placed upon the results of their use. Our most satisfactory procedure has been to prepare films according to the older method above named, and, when occasion demands, to supplement them by the use of the Graham-Cole test. The latter test may be employed either orally or intravenously; or, in selected cases, by both methods in succession. This combined use has enabled us, in certain instances, to interpret the films of the gall bladder correctly when one method alone was inconclusive.

When the dye is administered orally the problem of intestinal absorption enters. No difference in absorption has been noted by us when the dye is given dissolved in some medium, such as grape juice, or when it is given in the form of properly prepared capsules. Nonfilling or incomplete filling of the gall bladder may be due to lack of dye absorption rather than to disease of the gall bladder itself. Satisfactory filling is, on the other hand, not infrequently found in pathologic gall bladders. In spite of the fact that the intravenous administration of the dye consumes more time and occasionally causes unpleasant reactions, it has proved, in our experience, the more satisfactory method, because the disturbing factor of intestinal absorption is removed. However, a pathologic gall bladder may give a normal response to either method.

TABLE I.—TABULATION OF PATIENTS EXAMINED FOR CHOLECYSTITIS
(OCTOBER, 1922, TO OCTOBER, 1927).

	No.
Patients examined for gall bladder disease	4820
Patients diagnosed cholecystitis	1332
Patients studied and operated upon for gall bladder disease	459

These observations, as an analysis of the subjoined tables shows, are founded on the study of 4820 cases in which the gall bladder was investigated, and in which cholecystitis was diagnosed 1332 times. Of the 1332 patients in whom cholecystitis was diagnosed, 459 patients submitted to operation. The remaining 873, excepting the 23 patients tabulated (Table IV, 2) were persons who either declined surgical treatment or who seemingly did not need it.

TABLE II.—FACTORS UPON WHICH CLINICAL DIAGNOSIS IS MADE
(OCTOBER, 1922, TO OCTOBER, 1927).

Clinical diagnosis made by (together with associated data):

A. Direct evidence:	No.	Per cent.
1. + shadow	123	26.8
2. ++ shadow	185	40.3
3. +++ shadow	109	23.7
4. No shadow and unsatisfactory	42	9.1
(a) Before use of dye	28	6.0
(b) Evidence by oral dye	3	0.6
(c) Evidence by intravenous dye	11	2.4
5. Direct shadow identified by:		
(a) Oral dye	47	
(b) Intravenous dye	20	
B. Indirect evidence:		
1. Motor disturbances	438	95.4
Absence of motor disturbances	21	4.6
2. Deformity of antrum or duodenum:		
(t) Bands	100	22.0
(b) Ulcers	61	13.4

In studying the films made without the use of dye (Table II) we noted varying densities of the gall bladder shadows. Shadows that were quite faint, yet plainly visible and constantly present, we graded as 1+; shadows the density of which nearly equaled the shadow cast by the liver we designated as 4+. Between these two extremes of density there were many gradations, which we grouped under the heading of 2+, and which obviously formed the largest group. Comparison of the density of the gall bladder shadow on the film with the surgeon's report as to the size of the gall bladder and thickness of the wall, was instructive. We noted that many of the cases showing 1+ shadow densities on the film were reported as having very thick walls or a viscid bile content; whereas the 4+ shadows were frequently found in gall bladders that were thin-walled and easily compressed. This observation led to the chemical analysis of the gall bladders reported here.

It is significant that in only 9.1 per cent of the cases of gall bladder disease the direct study was unsatisfactory. It will be

noted (Table II, A-4) that 6 per cent of the cases unsatisfactorily examined occurred before dye methods of study were adopted. With the advent of the use of tetraiodophenolphthalein it became possible to eliminate this group of unsatisfactory examinations. Thus in two groups of cases distinct aid was obtained from the Graham-Cole test: One in which no shadow appeared on the direct film, and in which subjective symptoms and the presence of indirect evidence made further study necessary; and one in which the multiple shadows required differentiation.

In addition to the study of the direct films of the gall bladder, observation of the opaque meal in the stomach, duodenum and colon yielded information of equal importance. In nearly 100 per cent of patients having pathologic gall bladders there was some form of motor disturbance or deformity of the gastrointestinal tract. These disturbances of function and contour assumed many forms. The most common form was spasm of the gastric antrum, the bulb, and the duodenum. Next in frequency was deformity of the gastric antrum, the bulb, or the duodenum, and less frequent was reverse peristalsis in the duodenum and fixation of the hepatic angle of the colon.

Disturbances of the normal peristaltic gradients, observed fluoroscopically, were very important findings. These disturbances were present in every case of cholecystitis studied during a period of distress. Deformity of the gastrointestinal tract observed during examination was found at operation to be due to: (1) Perivesicular inflammation; (2) congenital bands or membranes; (3) coëxistent ulcer; (4) periduodenal inflammation from pancreatitis; and (5) persistent tonic spasm. As spasm was not often found at operation, many deformities due to spasm seen on the fluoroscopic screen were not verified by the surgeon.

Stones (Table III) were demonstrated in 60.6 per cent of the cases found to have stones at operation. This percentage is about the figure given by Cole in 1915. Patency of the common duct, as evidenced by regurgitation of barium, was seldom seen.

The first item of Table IV shows the surgeon's opinion of the gall bladder in 44 cases operated upon for abdominal disease other than that of the biliary tract. In these cases gall bladder studies had been made by us and normal findings reported. 2a shows an analysis of the 23 cases in which a roentgenologic diagnosis of cholecystitis was made and in which surgical opinion negatived removal of the gall bladder. Considering that of these 23 patients, 8 failed to receive postoperative relief and 1 received relief only after a subsequent removal of his gall bladder, we may draw the conclusion that our diagnoses of these cases were correct. Our percentage of correctness is then 97.1. If, however, these 9 patients represent no surgical error in diagnosis, our percentage of correctness falls to 95.2.

TABLE III.—INCIDENCE OF PANCREATITIS, STONES AND PATENT COMMON DUCT.

	No.	Per cent.
Pancreatitis	23	5.0
Stones	181	39.4 (60.6)
(a) Positive shadows	103	56.9
(b) Negative shadows	7	3.9 (60.8)
(c) Not found	71	39.2
Patent common duct	5	1.9

TABLE IV.—CLINICAL AND OPERATIVE FINDINGS IN THE SERIES.

	Times.
1. Gall bladder, negative Roentgen ray, negative at operation (operated for other lesions)	44
2. Gall bladder, positive Roentgen ray, negative at operation	23
2a. End results in 23 patients, gall bladder not removed:	
Symptoms relieved	11
Symptoms not relieved	8
Gall bladder subsequently removed and symptoms relieved	1
Cases associated with ulcer	4
Cases not traced	3
3. Gall bladder, negative Roentgen ray, positive at operation (each case associated with duodenal ulcer)	4
4. Diagnosed chronic cholecystitis	1332
Operated upon for chronic cholecystitis	459*
5. Total gall bladder operations	459
Explored and not removed	23
	<hr/> 482
Per cent diagnosed correctly	95.2 97.1
Per cent diagnosed incorrectly	4.8 2.9
6. Operative deaths, 7 (459 cases)	1.5
Operative deaths, 8 (666 cases)	1.20

* 42 per cent.

TABLE V.—INFLUENCE OF DYE METHODS (JANUARY 1, 1925, TO OCTOBER 1, 1927).

	No.	Per cent.
Patients examined for gall bladder disease	2161	
Patients examined and operated upon for gall bladder disease	292	
Direct evidence alone	171	58.5
Supported by oral dye (all cases)	78	26.7
Supported by intravenous dye (all cases)	25	8.5
Unsatisfactory; diagnosis made by:		
(a) Oral dye	1	0.34
(b) Intravenous dye	11	
Unsatisfactory; no dye used	5*	
Negative; dye negative; operation positive	1	
	<hr/> 292	
Nonfilling by oral method; filling by intravenous method		4
Nonfilling by oral method; nonfilling by intravenous method		4
Oral and intravenous methods checked		3

* 2 of which were ulcer cases.

In January, 1925, we first used cholecystography, and from that date until October, 1927 (Table V) the dye was employed in 41.4

per cent of the 292 cases later operated upon. The new technique was solely responsible for the roentgenologic opinion in only 0.4 per cent of these cases. In order to test the accuracy of the two methods of dye administration, a group of patients was given the dye by both methods, and 11 of these were operated upon. In 4 of these there was no filling after oral administration of the dye, and good filling after intravenous injection. Four showed no filling with either method and 3 showed filling with both methods.

Inorganic Chemistry of the Normal and the Pathologic Gall Bladder and Its Bile Content (R. B. Adams). At the suggestion of the authors of the present study, a series of normal gall bladders with their bile content, obtained from unembalmed bodies after accidental death, and a series of pathologic gall bladders with their content, obtained at operation from some of the cases now under discussion, were subjected to a complete inorganic chemical analysis. The autopsy material was obtained by tying and cutting the cystic duct and dissecting the gall bladder away from the liver. In each series a small section of the duct and a small section of the fundus were removed, preserved in formalin and given to the pathologist for histologic examination. The specimens were examined for evidence of gross disease and weighed, after which they were placed in a drying oven at 105° C. for seventy-two hours, dried to a constant weight, cooled and weighed again. They were then ashed in fused silica crucibles and the ash weight recorded. The ash was treated with hot aqua regia, digested for an hour, cooled, diluted and filtered through ashless filter paper to determine the insoluble gangue. There was no significant amount of the latter, however, in any case.

The filtrate was then further diluted, neutralized with NH_4OH heated to boiling and treated with an excess of NH_4OH , to determine the iron group. The latter was not subjected to further detailed analysis owing to the fact that the small amounts obtained rendered the procedure impracticable.

The filtrate was treated at the boiling point with an excess of oxalic acid, and after an hour was filtered on ashless paper to determine the calcium oxalate. Owing to the large volume of the solution, the high concentration of NH_4Cl and the small amounts obtained, it was not considered necessary to redissolve and reprecipitate this group, as error from this source would be negligible for the purpose of the present study.

The precipitation of magnesium, as magnesium phosphate, yielded in no case a weighable precipitate. No other elements or groups of elements have been reported in sufficient quantities to make them important.

In all, 10 presumably normal gall bladders and contents, obtained from autopsies, and 14 pathologic gall bladders and contents, obtained at operation, were subjected to analysis. They were all

TABLE VI.—SHOWING THE INORGANIC CHEMICAL ANALYSES OF NORMAL GALL BLADDER AND CONTENTS.

Normals.	Total wet weight.	Dry weight.	Per cent of wet weight.	Ash.	Per cent of weight.		Fe.O ₃ .	Per cent of weight.		CaO.	Per cent of weight.	
					Wet.	Dry.		Wet.	Dry.		Wet.	Dry.
1.	...	8.7520	...	0.3488	...	3.98	0.1524	...	1.76	0.0020	...	0.023
2.	...	12.8380	...	0.5244	...	4.08	0.0926	...	0.72	0.0032	...	0.025
3.	...	16.2300	...	0.6482	...	4.25	0.1110	...	0.73	0.0036	...	0.024
4.	...	12.9600	...	0.2564	...	1.98	0.0454	...	0.35	0.0102	...	0.079
5.	...	21.6420	...	0.8444	...	3.89	0.2084	...	0.96	0.0028	...	0.013
6.	19.7070	8.7540	44.40	0.4204	2.250	4.81	0.0820	0.4200	0.94	0.0044	0.022	0.050
7.	24.4122	9.5632	39.10	0.4114	1.680	4.30	0.0538	0.2200	0.56	0.0022	0.009	0.023
8.	56.6038	16.4820	29.10	0.6320	1.120	3.84	0.0770	0.1400	0.47	0.0112	0.020	0.068
9.	155.2000	12.8038	8.25	1.1038	0.710	8.63	0.0990	0.0640	0.77	0.0062	0.004	0.048
10.	32.2932	10.6632	33.00	0.4544	1.410	4.25	0.1010	0.3100	0.95	0.0042	0.013	0.039
11. Bladder only	16.0140	0.0508	0.317	...	0.0068	0.0425	...	0.0028	0.017	...
Total, except No. 11	288.4160	129.6882	153.90	5.6442	7.170	44.01	1.0226	1.1500	8.21	0.0550	0.068	0.392
Average, except No. 11	57.68	12.9688	30.8	0.5644	1.43	4.40	0.1023	0.2300	0.82	0.0050	0.014	0.039

Average CaO per cent dry weight for Cases 1, 2, 3, 5 and 7, 0.0216.

TABLE VII.—SHOWING THE INORGANIC CHEMICAL ANALYSES OF DISEASED GALL BLADDER AND CONTENT.

No.	Tissue.	Total net weight.	Dried at 105°C.	Per cent of wet weight.	Ash, weight, gm.	Per cent of weight.		Fe ₂ O ₃ , weight, gm.	Per cent.		CaO, weight, gm.	Per cent.		MgO.	Shadow.
						Wet.	Dry.		Wet.	Dry.		Wet.	Dry.		
10480	Bladder	5.4186	1.8556	34.30	0.0458	0.846	2.47	0.0012	0.0222	0.0650	0.0030	0.0550	0.162	Trace	4+
	Bile	18.9528	3.0918	16.30	0.2188	1.150	7.08	0.0220	0.1160	0.7120	0.0042	0.0220	0.136	Trace	
10750	Bladder	3.6446	1.1814	32.50	0.0166	0.456	1.40	0.0010	0.0270	0.0845	0.0012	0.0330	0.101	Trace	2+
	Bile*														
10518	Bladder	3.7650	0.9360	24.86	0.0266	0.707	2.84	0.0042	0.1110	0.4500	0.0012	0.0318	0.128	Trace	4+
	Bile	9.8150	0.9234	9.40	0.1042	1.060	11.30	0.0080	0.0815	0.8700	0.0018	0.0183	0.195	Trace	
10547	Bladder	6.7154	1.3123	19.57	0.0380	0.570	2.90	0.0026	0.0390	0.1980	0.0020	0.0300	0.152	Trace	4+
	Bile	21.3836	2.5078	11.70	0.2448	1.150	9.77	0.0224	0.1050	0.8930	0.0010	0.0470	0.400	Trace	
13793	Bladder and bile	47.4332	10.6372	22.40	0.5594	1.180	5.25	0.0380	0.0800	0.3560	0.0052	0.0110	0.049	Trace	2+
13719	Bladder and bile	10.4668	3.7560	35.80	0.1040	0.990	2.77	0.0028	0.0270	0.0750	0.0012	0.0120	0.032	Trace	1+
5841	Bladder and bile	20.2532	7.8426	38.70	0.2256	1.110	2.88	0.0092	0.0450	0.1170	0.0038	0.0190	0.049	Trace	2+
14041	Bladder and bile	16.9080	5.9482	35.10	0.2460	1.450	4.15	0.0296	0.1750	0.4980	0.0124	0.0730	0.209	Trace	4+
13897	Bladder and bile	11.7500	5.5800	47.50	0.1024	0.870	1.84	0.0094	0.0800	0.1680	0.0038	0.0320	0.068	Trace	2+
14128	Bladder and bile	2.9200	2.9200	19.50	0.1630	1.090	5.58	0.0098	0.0660	0.3360	0.0036	0.0240	0.123	Trace	4+
14286	Bladder and bile	52.5900	9.5400	18.10	0.6320	1.200	6.62	0.0750	0.1440	0.7960	0.0032	0.0060	0.032	Trace	2+
10041	Bladder and bile	8.3982	1.6282	19.40	0.0838	1.000	5.15	0.0040	0.0520	0.2700	0.0022	0.0260	0.135	Trace	4+
14181	Bladder and bile	11.9900	1.8600	15.50	0.0946	0.790	5.09	0.0110	0.0920	0.5920	0.0028	0.0230	0.150	Trace	4+
14150	Bladder and bile	9.7480	2.1320	21.90	0.1004	1.030	4.72	0.0040	0.0410	0.1880	0.0046	0.0470	0.216	Trace	2+

Assumed normal gall bladder and bile CaO per cent dry weight, 0.02.

Assumed 2+ gall bladder and bile CaO per cent dry weight, 0.05.

Assumed 4+ gall bladder and bile CaO per cent dry weight, 0.16.

* Duct was not tied off and bile was all in bottom of bottle.

subjected to the same procedure during the same period of time and with the same reagents and apparatus in order to have the results comparable, if not strictly accurate in all respects. The percentage of ash, etc., was calculated on both the wet and the dry-weight basis, the latter being used for comparison, as it was considered more uniform than the former. The bladder wall and the bile content separately yielded very similar percentage results, so that they were combined as a unit. The details of the analysis are given in Tables VI and VII. Cases 4, 6, 8, 9 and 10 in Table VI were arbitrarily thrown out from the presumably normal gall bladders because they were obtained from older subjects and histologic examination showed some tissue change. The series consisting of Cases 1, 2, 3, 5 and 7 yielded an average of 0.0216 per cent Ca as CaO. The average percentage of the iron group reported as Fe_2O_3 was 0.82 for the normal series and only 0.34 for the pathologic series.

Comment. For the correlation of the analytical data obtained by Dr. Adams with the gall bladder shadows obtained by us on the direct films in the pathologic series, the films were first read and the shadows recorded in terms of 1+, 2+ and 4+ density, as previously explained. With these records made, and in order to avoid biased judgment, Dr. Adams was called in to read the figures of his analyses. The results are given in Table VII. It is interesting to note that in regard to CaO the per cent dry weight averaged 0.02 for the supposedly normal gall bladders, 0.032 for the one gall bladder giving a shadow recorded as 1+, 0.05 for those giving shadows recorded as 2+ and 0.16 for those giving shadows recorded as 4+. It seems evident that as the calcium content increases, the denser becomes the shadow produced by the gall bladder on the film. We are not able at present to give an explanation for this fact, nor to ascribe any significance to it. We have been unable to reproduce, by means of various media, shadows graded as to density by using corresponding dilutions of calcium salts. The percentage of calcium content is very small in all instances, and it may be that the density of the shadow depends upon other factors than the percentage content of the calcium itself. However, this small variation in calcium content may possibly lead to a better understanding of shadow production in the future.

Part II. The Application. Our approach to the subject of chronic cholecystitis has extended over a period of nearly twenty years. During this time three noteworthy events appeared chronologically in the development of the opinions here expressed. These events were the response of persons to forced feeding under control, the publication by Alvarez³ of the gradient theory of peristalsis, and later the development by George and Leonard of a technique which permitted the recognition of the gall bladder upon Roentgen films.

The first came to us while correlating the principles that underlie

the reconstruction of the general asthenic body. These principles are: (1) The regulation of the gastrointestinal tract by means of diet; (2) addition of sufficient body weight by forced feeding; (3) reconstruction of the body by means of corrective exercises and general physical training; (4) establishment of a sufficient fund of body reserve strength and the fixation of a new body habit. Often while working with asthenic patients we found it impossible to regulate the bowel, and forced feeding produced repeated upsets with distress, nausea and vomiting. Gradually experience taught us that some surgical barrier, impossible to recognize, existed in the abdomen, and that when this surgical barrier was removed the bowel could be regulated and the patient could consume large amounts of food without discomfort.

The most frequent surgical barrier found in these patients was chronic disease of the gall bladder. Other lesions were peptic ulcer, chronic appendicitis, less frequently tuberculosis and rarely an irrelievable intestinal stasis. This experience led us frequently to employ the "therapeutic test" in chronic borderline abdominal cases. The patient was placed in hospital under control with heavy forced feeding. If his abdominal symptoms disappeared quickly, if his bowel became regular under the influence of the diet, and if he became more comfortable, it was concluded that he did not have local abdominal lesions of surgical import. Few mistakes were made by following this procedure and no harm came to those patients who had surgical abdominal lesions. It is to be recalled that in these earlier years, 1908 to 1914, most cases of cancer, ulcer and local kidney disease, were found by the diagnostic methods then employed and did not enter into this group of borderline cases. Moreover, at the time of the upset it was found by roentgenologic examination that spasm of the antrum, the pylorus and the duodenum, and, oftentimes, reversed peristalsis of the duodenum, were present. In two or three days' time, under the influence of an ulcer régime, the spasm disappeared, and the patient became comfortable, but an upset could be reinduced as often as heavy forced feeding was resumed. The explanation of the antral and duodenal spasm observed with the associated symptoms of gas distress, pain, nausea and vomiting, came to us in 1915 in the publication by Alvarez of his theory of intestinal gradients and of his views on the syndrome of mild reverse peristalsis. The theory of gradients explained our clinical problems so completely that, in spite of the fact that for some years other physiologists seemed loath to give credence to it, and it is still held tentatively, the theory has continued to influence more and more our clinical work in gastroenterology. We assumed that the presence of a motor disturbance at the end of the stomach indicated some form of lesion in that neighborhood, and that the diagnosis was not made until the lesion could be identified. The gradient theory offered an explanation for the "ulcer syndrome"

seen occasionally in cases of cholecystitis or appendicitis; it explained the variability of the symptoms in lesions of the digestive tract. It explained the similarity of symptoms with different lesions, and also the absence of symptoms in many cases of abdominal disease. There was no question about the existence of physiologic gradients in the heart, the digestive tract and in other hollow tubes, such as the ureter, and we felt that the time had come for clinicians to make clinical use of the theories to be derived from the presence of these gradients. In consequence, this work became the second noteworthy step in our approach to the subject of chronic cholecystitis.

The third step to the problem of chronic gall bladder disease came in the publication in 1922 of the monograph by George and Leonard on the pathologic gall bladder. Numerous articles on the roentgenologic recognition of the diseased gall bladder had been made prior to this time. Cottell (1896) and Beck (1899) had reported the ability to see stones; Rieder (1904) and, especially to be mentioned, Pfahler (1911), and later Case (1913) and Cole (1914) had all laid stress upon the so-called "indirect" evidence of gall bladder disease. But it was the work of George and Leonard that incited us to begin a systematic correlative study of both "direct" and "indirect" evidence. The indirect evidence of pressure effects and of distortions by traction appeared to us to be of less moment than the so-called reflex effects, the motor disturbances, the disturbed metabolic gradients. Cholecystography, the epochal work of Graham, Cole and Copher (1924), which now dominates the diagnostic field, has not proved so useful in our hands. It has been used only as stated above, and as reference to Tables II, IV and V indicate in detail, as a confirmatory means of recognizing the shadow of the gall bladder on the direct films in more or less doubtful instances.

Diagnosis. The diagnosis of the chronically diseased gall bladder has been made, in the course of this study, by both the direct and indirect evidence in each patient. This statement means that a distinctly clean-cut recognizable shadow of the gall bladder is sought, and usually obtained, upon the direct film, and that, at the same time, some form of motor disturbance about the end of the stomach or duodenum is seen. The latter evidence is seldom found wanting—it was absent in only 4.6 per cent. We believe it would be found in all cases if the examination were made at the time of distress. Before we made use of dye methods we were unable to obtain shadows upon the direct films in 8.4 per cent of the cases, and after we employed dye methods only 4.1 per cent depended upon the dye for recognition. It is true that the technique required for visualizing the gall bladder on direct films is more particular and the labor more arduous, but the final results—95.2 to 97.1 per cent correct diagnoses, depending upon the interpretation of item 5, Table IV—would seem to justify the added effort.

Selection of the Surgical From the Nonsurgical Case. It is obvious that with the perfection of accurate methods of recognizing the chronically diseased gall bladder, the former opinion of the surgeon that all gall bladder disease is essentially of surgical nature is not tenable. Postmortem statistics of the pathologist are well corroborated by those of the present-day roentgenologist. The diagnosis of chronic cholecystitis today cannot carry with it the expectation of surgical treatment alone. In our present series 1332 diagnoses of chronic cholecystitis were made between October, 1922, and October, 1927. Of this number, only 459 (42 per cent) underwent some kind of gall bladder operation. The remaining 58 per cent were given relief for the most part by dietetic and other measures. The temperament of the patient enters somewhat into the problem of treatment. Some persons, rather than carry on a dietetic régime, welcome an operation in the hope of obtaining immediate relief. Undoubtedly some of the 459 patients, had they so wished, might have avoided operation. On the other hand, the common dread of operation has given us the opportunity to determine whether relief of symptoms could be obtained under dietetic control in some patients who, we at first thought, should be treated surgically. In a number of patients distress was severe; in some gall stones had been recognized; yet complete relief was given by removing the motor disturbance with a smooth, regulatory diet. The patient understood that if he did not continue to obtain relief, his only recourse would be an operation. It has been interesting to note that few of these patients have returned for operation.

The segregation of the nonsurgical cases, therefore, has been made according to the functional response to dietetic control. In most instances the patient may be first given directions to carry out at home. If he is unable to obtain relief in this manner, and is able to bear the expense of two or three weeks of hospital treatment, he is placed in hospital, and his response to treatment under control is ascertained. If he obtains relief from his symptoms, and, at the same time, the spasm about the end of the stomach disappears, he is trained in the art of stomach and bowel regulation and sent home to continue the régime. If, on the other hand, he is upset; if he suffers distress from bloating; if nausea and vomiting are produced; if the antral or duodenal spasm with reversed peristalsis is increased, he is considered of necessity a surgical case, for experience has taught us to place much confidence upon this test. We feel justified, in the presence of two or three produced upsets, in giving the patient a choice between continued distress and an operation. In the years we have been testing patients in this manner we have seen the subsidence of symptoms accompany the disappearance of the motor disturbances at the end of the stomach and throughout the bowel. When the distress recurs the motor disturbances are found to be present at the same time. The two go together with

such uniformity that it is reasonable to conclude that the distress is the result of the disturbed peristalsis.

When the patient is dismissed with dietetic directions alone he is told that occasionally mild cholecystitis cases develop acute complications, as suppurative cholecystitis and secondary pancreatitis, which demand immediate care; but he is assured that the percentage of such complications is not great, and that his dietetic measures may possibly prevent them.

TABLE VIII.—POSTOPERATIVE END-RESULTS IN 603 CASES OF CHRONIC CHOLECYSTITIS AND DURATION OF SYMPTOMS IN THE BROAD- AND ASTHENIC-BUILT PATIENT.

	No.	Broad.		Asthenic.	
		No.	Per cent.	No.	Per cent.
Practically free immediately	133*	119	28.0	14	8.0
One or two relapses	14	9	2.0	5	3.0
Duration:					
1 month	4	3	1.0	1	0.5
2 to 3 months	21	16	4.0	5	3.0
4 to 6 "	44	32	7.5	12	7.0
1 year	42	29	7.0	13	7.5
1 to 2 years	16	10	2.0	6	3.5
2 years and over	64	41	9.5	23	13.0
Symptoms:					
Continuous	25	16	4.0	9	5.0
Periodic	116	75	17.5	41	23.0
Mild, less than before operation	83	55	12.5	28	16.0
Severe, equal to or greater than before operation	41†	25	5.0	16	9.0
Total	603	430	71.3	173	28.7

* 22 per cent (78 per cent).

† 7 per cent.

Postoperative Medical Treatment. As with the preoperative case of mild chronic cholecystitis, so with the case operated upon, the presence or absence of continued or periodic distress depends for the most part upon the presence or absence of motor disturbances of the gastrointestinal tract. Table VIII gives a postoperative end-result analysis of 603 cases. Only 22 per cent of the patients were relieved of the distress for which they were operated upon within the period of surgical convalescence. Seventy-eight per cent continued to have distress of variable intensity over periods of time ranging from a month to more than two years. With some patients the symptoms were more severe and more persistent than before operation. Most of the latter group were returned to the medical hospital for subsequent treatment, some patients as many as three or four times, before relief became permanent. Two factors seemed to be of importance in bringing about ultimate relief, the first being freedom from motor disturbances, as already described, and the second the associated influence of a general asthenic state. Although chronic gall bladder disease is much more prevalent in persons of

the broad or sthenic type of build—71.3 per cent in the series as compared with 28.7 per cent in persons of asthenic build—yet the relief of symptoms on the whole in the patient of broad build is quicker and more complete than in the one of narrow build. Of the broad-built, 28 per cent received immediate relief, whereas of the asthenic-built, only 8 per cent received like results. Many of the asthenic-built patients had to be reconstructed according to the four principles enumerated above before relief was obtained. But oftentimes in the broad-built patient, as well, gymnasium work, horseback riding, etc., played an important rôle in the ultimate cure.

In the study of surgically treated patients under control in hospital we noted the same relationship between the presence of motor disturbances of the stomach and duodenum and the presence of symptoms as were found in patients not operated upon. The absence of symptoms seemed to accompany at all times the absence of antral and duodenal spasm. In the exceptional case in which relief was not obtained subsequent operation revealed the presence of an overlooked stone. Adhesions about the duodenum and surrounding viscera played no part in the postoperative failure in this series of cases. Distinct secondary pancreatitis was recognized only 23 times in 459 cases (5 per cent), a percentage lower than in most similar statistics. We have found no reason to agree with Bassler*, however, when he states that the pancreatic function is disturbed in most gall bladder diseases—67 per cent in his experience—and we have found no instance in which distinct fat stools followed the ingestion of fat in the diet, as reported by Else,⁵ or in which we could satisfy ourselves that the postoperative symptoms, as believed by Bassler, were related to pancreatic hypofunction.

The postoperative medical treatment has consisted, therefore, of the same dietetic methods of control and of the application of the same general reconstruction principles employed in those patients who found relief from symptoms without the assistance of surgery. The patient who contemplates an operation is told frankly that he must expect more or less distress to remain for a time after operation, but that he can be eventually relieved by following the above régime. By this postoperative control of the patient have we justified, in our own minds, the increased amount of gall bladder surgery which the newer methods of diagnosis have brought about, and the many apparent postoperative failures have been given a new understanding. The diseased gall bladder is considered, by reason of the local symptoms, a local barrier, which, in certain instances, must be removed in order to remove disturbances of peristalsis.

* Dr. A. H. Aaron reported, before the American Gastroenterologic Association, May 6, 1929, observations on the enzymatic concentration in the duodenal contents in a group of 50 cases over a period of three years. The gall bladder cases showed but little variation from normal figures both before and after cholecystectomy.

In 63 cases of combined cholecystitis and peptic ulcer (Table IX) the same principles of postoperative treatment have been followed. A greater number of patients obtaining immediate relief from operation is noted in this series than in the series of uncomplicated cholecystitis. The cause of this result is not apparent. Possibly the ulcer is the dominant lesion and operation for the ulcer removes the opportunity for recurring spasm. Spasm, however, is by no means removed in all cases, and the ultimate recovery of the patients of this group has not been uniformly as good as that of the patients with uncomplicated cholecystitis. In this series of patients, likewise, the influence of the constitutional factor is noted as it was in the other series.

TABLE IX.—POSTOPERATIVE END-RESULTS IN 63 CASES OF CHRONIC CHOLECYSTITIS AND ULCER, SHOWING DURATION OF SYMPTOMS IN THE BROAD- AND ASTHENIC-BUILT PATIENT.

	Total	Broad.		Asthenic.	
		No.	Per cent.	No.	Per cent.
Practically free immediately	30	22	55.0	8	35.0
One or two relapses	2	2	5.0		
Duration:					
1 month					
2 to 3 months					
4 to 6 "	1	1	2.5		
1 year	7	3	7.5	4	17.0
1 to 2 years	3	2	5.0	1	4.0
2 years and over	3	1	2.5	2	8.5
Symptoms:					
Continuous	4	2	5.0	2	8.5
Periodic	6	4	10.0	2	8.5
Mild, less than before operation	6	3	7.5	3	13.0
Severe, equal to or greater than before operation	1	1	4.5
Total	63	40	63.5	23	36.5

To the usual two weeks' postoperative surgical treatment we have advised all patients operated upon to add a week or ten days of dietetic training in the medical hospital. As not all patients, for financial or other reasons, have done so, we have observed, by comparison, quicker convalescence and greater freedom from distress in the patients so trained.

Causes of Operative Failure. It is evident from what has been said in the foregoing paragraphs that, in the present series of cases under discussion, the only important cause for an operative failure of relief of symptoms has been the continued motor disturbance along the gastrointestinal tract. Into this problem of disturbed peristaltic gradients a general asthenic state has many times entered. Relief of the one and reconstruction of the other has led finally to good postoperative end results. In 2 cases an overlooked common duct stone led to reoperation. Adhesions between surrounding viscera and the gall bladder, or its former site, produce for the most

part reflex disturbances of peristalsis—disturbances which are functional in character, and can, in consequence, be relieved. Only rarely do adhesions in the upper abdomen become obstructive in character. Hepatitis may have existed, in greater or less degree, in all of the cases. In certain cases associated with a fixed secondary or a borderline anemia, sections removed from the liver for histologic and bacteriologic study showed the presence of chronic infection. In two or three instances of apparently progressing chronic obstructive biliary cirrhosis the patients have remained in poor health. The use of the "therapeutic test" has been of distinct value in some of our postoperative cases in showing that relief of symptoms was possible and that the actual surgical barrier had been removed.

Summary. 1. A clinical study of a considerable number of cases of chronic cholecystitis has been made for the purpose of correlating the "direct" and the "indirect" evidence of the presence of gall bladder disease. It has been shown that the proper correlation of these factors leads to a remarkably accurate clinical diagnosis of gall bladder disease—95 to 97 per cent correct diagnoses.

2. A method is given by which, with a high degree of safety, cases of chronic cholecystitis which should be considered surgical in type may be segregated.

3. Based upon the metabolic gradient theory of peristalsis, a logical explanation is given for the presence of most of the preoperative symptoms of chronic cholecystitis and also for the presence of the same symptoms remaining after operation. A workable method of postoperative medical treatment, based upon this theory of peristalsis and upon the constitutional type of the patient, is also given.

4. The CaO content of the gall bladder wall increases in percentage, for some unknown reason, as the gall bladder increases the density of its shadow upon direct Roentgen films. The content varies from an average of 0.02 per cent CaO dry weight in presumably normal gall bladders, which cast no shadow upon the direct film to an average of 0.16 per cent CaO dry weight in those gall bladders which cast a dense shadow upon the direct film. No explanation is given for this finding, and its relation, if any, to shadow production on the direct film has not been determined.

BIBLIOGRAPHY.

1. George, A. W., and Leonard, R. D.: *The Pathologie Gall Bladder: A Series of Monographie Atlases*, New York, Paul B. Hoeber, Inc., 1922, vol. 2.
2. Case, J. T.: *Radiology*, 1928, 2, 1.
3. Alvarez, W. C.: *The Syndrome of Mild Reverse Peristalsis*, J. Am. Med. Assn., 1917, 69, 2018. See also Vols. 1 to 11, Collected Reprints, Hooper Foundation, University of California, and *The Mechanics of the Digestive Tract*, 2d ed., New York, Paul B. Hoeber, Inc., 1928.
4. Bassler, A.: *Ann. Int. Med.*, 1928, 2, 192.
5. Else, J. E.: *Northwest Med.*, 1928, 27, 145.

A CLINICAL STUDY OF VISCEROPTOSIS.

BY BLANTON P. SEWARD, A.B., M.D.,

ROANOKE, VA.

(From the Department of Medicine, Lewis-Gale Hospital.)

GLÉNARD's description of the visceral ptoses in 1885 has been followed by many articles on that subject. A number of them have added to our knowledge; those of Goldthwaite¹ and White² dealing with the orthopedic element in visceroptosis being especially interesting. It appears to the writer that none of the articles, whether in textbooks or in journals, gives adequate consideration to this condition, as one gains the impression from them that visceroptosis is merely a manifestation of a general constitutional weakness and is of little significance. The character of the symptoms ptosis may cause, the similarity which the symptoms may bear to those of organic disease, and the effect of ptosis upon the efficiency of the individual are not emphasized. It is for this reason that we shall attempt a discussion of visceroptosis.

Prior to the discovery of the Roentgen ray the position of the viscera was determined by studying their relationship in the cadaver. The use of the Roentgen ray in studying the skeleton, body cavities, and viscera in the human being has given much information concerning the relationship between the size, position, and motility of the viscera to body form. As a result of these studies we have learned that there are variations from the theoretically normal body previously described, and from this information we have deduced specifications of certain general body types which may be regarded as normal. The physician who is interested in form, and who recognizes that form and function are different phases of the same vital process, can appreciate the differences existing in persons of various body types. The lack of appreciation of these differences in types is the cause of the failure of many therapeutic measures.

In 1917 Mills,³ in submitting a classification of body types, described the sthenic and the asthenic as the dominant ones. According to this classification, the sthenic group is characterized by a thick, broad, short thorax, a long abdomen of great breadth in the upper portion, and a relatively small pelvis, padded with fat. The asthenic group is characterized by frailty of build, a long, narrow thin chest, a short thin abdomen, and a relatively wide and capacious pelvis. To these groups Mills added the hypersthenic and hypoasthenic subdivisions. We adopted this classification and have found a fairly constant relationship between body type and the size, position and motility of the viscera. For example, a thorax or abdomen with certain anatomic characteristics can, of necessity, accommodate organs of certain form and in certain positions. Under

the fluoroscope the stomach of both the sthenic and the hypersthenic person is seen lying well above the interiliac line; while in the asthenic and hypoasthenic person, all of the organs are low with either the stomach or the transverse colon, and frequently both, lying in the pelvis. Changes in the rate of peristalsis also are often observed in the latter group.

The body habitus must be considered before a diagnosis of ptosis can be made. For instance, if in a sthenic person the lowest point of the greater curvature of the stomach is below the interiliac line; or if the transverse colon lies in the pelvis, we consider the position of those organs to be below the normal level for that type. Studies of the asthenic type confirm the belief that only with a considerable elongation of the stomach—the greater curvature lying well below the line between the iliac crests, or the transverse colon lying low in the pelvis—is a diagnosis of ptosis permissible. With these arbitrary rules in mind, we have approached this study of visceroptosis.

In order to understand the causes of ptosis, it is necessary to consider the anatomic factors concerned in maintaining the position of the viscera; for deviations from the normal create certain mechanical difficulties under which the gastrointestinal tract must work. The intestinal tract is held in position by: (1) The mesenteric attachments; (2) intraabdominal fat; (3) intraabdominal pressure and (4) the shape of the abdomen.

1. The mesenteric attachments: The intestinal tract, beginning at the second portion of the duodenum, is attached to the abdominal wall by the mesentery throughout its entire length. Since the large intestine is found more frequently to be abnormal in size and position, we shall speak only of the mesocolon. The ascending and descending colon and the hepatic and splenic flexures are attached to the posterior abdominal wall by the mesentery. The mesentery to the transverse colon is a thin, feebly supporting membrane. Coffey⁴ points out that failure of the right mesocolon to fuse properly with the parietal peritoneum predisposes to abnormal mobility of the cecum. In Waugh's⁵ opinion the abnormal mobility of the cecum and ascending colon leads to inefficient function and failure of peristalsis in that portion of the intestinal tract. Coffey also points out that the failure of the omental bursa to become obliterated weakens the feeble support of the transverse colon and more easily permits ptosis.

Probably the importance of the mesentery in supporting the weight of the bowel is less than its importance as a medium through which the nerves, blood and lymph vessels pass to the intestine. When excessive tension is imposed upon the mesentery by ptosis of the viscera, disturbances in the circulation of the blood are likely to result, the effect of which may be mild or sufficient to alter the circulation throughout the body.

2. Intraabdominal fat aids in the support of the gastrointestinal tract by acting as a cushion for the viscera and by increasing intra-abdominal pressure. Deposits of fat in the pelvis diminish the capacity of the lower abdominal cavity, and when the fat is absorbed a sagging of the viscera will take place.

3. Intraabdominal pressure is a negative pressure existing between the gastrointestinal tract and the osseomuscular walls. Wagoner's⁶ studies on this subject are of special interest as they show the effect of intraabdominal pressure on the function of the stomach and intestines. He measured the intraabdominal pressure in animals and in cadavers and found the pressure normally to vary from about -4 to -20 mm. of water. When he placed the experimental subjects in the upright position, the size of the abdominal cavity increased and the viscera gravitated to a lower level in proportion to the degree of emaciation and the relaxation of the abdominal muscles. As the cavity enlarged, the pressure within the abdomen increased tenfold in some of the animals while it increased from -20 to -106 mm. of water in the cadavers, the average increase being -52 . Wagoner⁷ found also by experiment that peristalsis is in a large measure dependent upon the relation between the pressure within the abdomen and the pressure within the intestine. For example, changes in intraabdominal pressure to a greater negativity resulted in a gradual diminution of peristaltic contractions. As the pressure in the dog exceeded -50 mm. of water, there was a gradual diminution in peristalsis until there was obliteration of all movement. If the intraabdominal pressure could be measured in visceroptotic patients, probably we would find that it often exceeds -50 mm. of water, and in the light of Wagoner's experiments we may expect peristalsis to be diminished in proportion to the increase in this pressure. A diminution in the rate of peristalsis promotes stasis of the intestinal contents, and sagging of the bowel, with a loss of tone of the involuntary muscles.

4. The shape of the abdominal cavity largely determines the position of the viscera. It is greatly influenced by the tone of the voluntary muscles, and the tone of the muscles is influenced by posture. The sthenic person has an erect posture; the tone of the abdominal muscles is good, and the viscera occupy mostly the upper abdomen. The asthenic person assumes a passive or stooped posture; the upper abdomen is often constricted; the distance from the umbilicus to the ensiform process is greater than the distance from the umbilicus to the side of the abdomen, and the abdominal muscles are relaxed. This relaxation increases the size of the lower abdominal cavity; causing the viscera to descend to a lower level when the individual stands.

There are two types of visceroptosis, the congenital and the acquired. The majority of the cases are congenital. An inherent structural weakness predisposes to ptosis which may be accentuated

by a long, slender body, relaxed tissues, failure of the right mesocolon to fuse with the parietal peritoneum, or of the omental bursa to become obliterated, poor muscular development, flattening of the lumbosacral curve, and faulty posture. As a result of the faulty posture and the deviations from the natural curves in the vertebral column the weight-bearing centers shift from their normal positions. Ptosis may be found also in patients with a more perfect body shape and posture. It may then be due either to a relaxation of the abdominal wall ensuing upon a debilitating sickness, poor habits, childbirth, to any condition causing prolonged strain upon the abdominal muscles, or to a developmental defect in the mesocolon.

Visceroptosis is encountered by the general practitioner, the internist, the surgeon, the orthopedist, and the obstetrician. There are three groups of persons with ptosis: First, those who have ptosis but who do not have symptoms; second, those who have ptosis and in addition have an organic lesion; third, those who have ptosis and whose symptoms are due to the prolapsed viscera.

Clinical Investigations. During the past two years we examined 37 patients whose symptoms were found to be due to visceroptosis. In that period also we examined a number of other patients who had, in addition to ptosis, an organic lesion in the gall bladder or some portion of the gastrointestinal tract. Some of these patients had symptoms due to the ptosis, but as the organic lesions were of primary importance, those patients were not considered in this study.

In the 37 patients we found ptosis of the stomach in 31; of the transverse colon in 26; of both the stomach and colon in 24; and a movable right kidney in 3. Nineteen of the patients were males; 18 were females, 8 of whom had borne children. The body weight of 28 patients was below normal for the age and sex. In 20 of the patients the ptosis was considered to be of congenital origin, and in 8 patients acquired. It was difficult to decide whether the ptosis was congenital or acquired in the remaining 9 patients since from the anthropometric examination they might have belonged to both the congenital and acquired classes. Each of the 9 patients was well proportioned, and it is possible that the prolapse of the viscera resulted from faulty posture or from prolonged physical strain. On the other hand, in 5 of these patients with a rather long decubitus we could see an approach to the slender type which may have predisposed to ptosis. The following table shows the age incidence:

TABLE I.—AGE INCIDENCE.

Years.	No. cases.
10 to 20	2
20 to 30	15
30 to 40	12
40 to 50	7
50 to 60	1

Gastrointestinal Symptoms and Findings. All of the patients had had "indigestion" for a period of a few months to several years; the average duration of symptoms was two years and ten months. The early gastrointestinal symptoms were few, consisting mainly of fullness after meals, flatulency and lethargy. As the abdominal muscles relaxed and the negative pressure within the abdomen increased, the motility of the gastrointestinal tract diminished in proportion to the increase in the negative pressure, as might have been expected from Wagoner's experiments mentioned above, the symptoms grew in number and became more generalized. There were variations in the symptoms depending upon the organ prolapsed, yet certain ones were common to all, such as a feeling of weight in the lower abdomen, a dragging sensation and backache, all of which were relieved by lying down. In addition to these sensations a number of patients complained of more or less constant pains in some region of the abdomen. The pain was in the lower right quadrant in 11 cases; under the left costal border in 7; in the upper right quadrant in 5; and in the center of the abdomen in 3 cases. The characteristics of the pains were: Irregularity of appearance during the day, and constancy in type in the individual cases. Conspicuous among the symptoms, especially in those patients with a low stomach, was a sensation of epigastric burning, which was relieved by food. When examined fluoroscopically the stomach often showed hyperperistalsis or hypoperistalsis; and frequently there was evidence of stasis in the colon, such as a delay in the passage of the opaque meal. Twenty-three patients complained of constipation, and in all of these the transverse colon was found, fluoroscopically, to be lying low in the pelvis.

Twelve patients showed normal acidity of the gastric secretion; 3 cases showed a mild hyperacidity; 5 showed an achylia; and in 3 of the patients with either hypoacidity or achylia, a dilatation of the second part of the duodenum was found. A mobile cecum with tenderness on palpation was noted in 14 patients.

Constitutional Symptoms. Symptoms such as drowsiness, dizziness, fainty sensations, dull headaches and inability to perform the day's work without feeling the need of rest were present in the majority of the patients. Mental and physical fatigue were prominent symptoms in the 14 patients who exhibited a systolic blood pressure of 110 or less. Five of the patients with hypotension showed also a postural hypotension, the systolic pressure falling from 6 to 12 mm. after they had stood for three minutes. This phenomenon may be explained by the accumulation of blood in the splanchnic vessels, particularly in the veins. The stasis of the blood probably accounts partly for the heavy, dragging sensation in the abdomen. The skin and mucous membranes presented an anemic appearance in the majority of patients with visceroptosis, though the erythrocyte count and hemoglobin content were moderately reduced in only fifteen.

Fourteen patients presented symptoms suggesting disturbances in the basal metabolic rate, which was found to be normal in 5; slightly increased in 5; while in 4 patients it ranged from -10 to -16 . The patient in whom the reading of -16 was obtained showed a marked gastroenteroptosis and delayed emptying time of the stomach on Roentgen ray examination. This patient, an unmarried girl, aged twenty-four years, ceased to menstruate two years previously and showed other evidences of endocrine disturbance, such as a moderate deposition of fat on the hips, but all of her symptoms were gastrointestinal. The clinical picture was that of myasthenia gastrica. In this case the visceroptosis was not the cause of the endocrine disturbance, though the latter was no doubt a factor in causing slow peristalsis.

Nervous Symptoms. Those patients whose symptoms were of a few years' duration often gave the impression of being neurotics or hypochondriacs. It is an easy matter for such persons to develop an introspective attitude as they usually worry easily. When their symptoms of "indigestion" and their "weak spells" continue after various remedies have been tried, they regard their symptoms seriously and the nervous element may eventually dominate the clinical picture. In some cases the inherent and allied deficiencies of the abdomen and central nervous system are manifested simultaneously; in others one of them predominates, and if absorption of toxic substances as a result of constipation are superimposed it is not difficult to imagine far-reaching results on an already unstable central nervous system.

Case Abstract. Six months ago an asthenic middle-aged woman came to the office complaining of "poor health and nervousness," which began eight years previously. During the first three years these symptoms were worse at intervals of two or three months, but were improved by a few days' rest in bed. In the past five years she had gradually grown weaker; the constipation had become more severe; the nervousness had increased; she was conscious of a dragging sensation in the abdomen; in fact, she felt "heavy all over" when standing or walking. In the past year she has not enjoyed her food as it caused her to feel "full and heavy;" she has been nauseated; she has been more nervous, and she was in bed fifteen weeks prior to the examination. She was discouraged because all methods of treatment had failed, including chiropractic adjustments.

Physical examination revealed relaxed abdominal muscles, evidences of visceroptosis, and a mobile cecum with tenderness on palpation. The Roentgen ray showed the greater curvature of the stomach lying 3 inches below the iliac crests and the transverse colon low in the pelvis. Gastric analysis showed achlorhydria, but other laboratory examinations, including the basal metabolic reading, were normal. She was treated for ptosis in the ways to be mentioned later, and improvement in all symptoms was noted in a few weeks, and within two months the patient was in better health and spirits than she had been for eight years.

It is not our intention to prove that visceroptosis is the cause of the vast number of symptoms of which a patient may complain.

Although visceroptosis cannot be considered pathologic in asthenic persons, yet many of them later will have symptoms of perverted physiology when the gastrointestinal musculature becomes atonic. However, ptosis of one or more viscera in a sthenic person may be regarded as pathologic. In either instance ptosis is often disregarded and the patient becomes a chronic complainer or has been one for a period of time.

Moody⁸ endeavored to determine the normal position of the abdominal viscera in persons of different types by Roentgen raying the gastrointestinal tract of 1000 university students. He found one or more viscera low in a large percentage of his subjects and he concluded that the diagnosis of enteroptosis, gastropptosis, and coloptosis are seldom or never justifiable. It should be remembered that his observations were made at the time of life when ptosis rarely causes symptoms. It would be interesting to learn the condition of those individuals ten or fifteen years later, when the strain and stress of life have taxed them. We believe a diagnosis of enteroptosis, gastropptosis, or coloptosis is justifiable since each denotes a specific relationship of the viscera to the body habitus.

Diagnosis. The points of distinction which should be stressed are: 1. The history of duration of the symptoms for months or years. During that time the symptoms have been persistent but not severe, whereas, organic lesions usually progress and the symptoms become correspondingly more severe.

2. Short intervals of a few days to two or three weeks of comfort after the symptoms have appeared as compared with longer intervals when the gall bladder or appendix is diseased.

3. The absence of the characteristic periodicity of the symptoms of duodenal ulcer.

It is rarely difficult to make a diagnosis of ptosis, though it is sometimes difficult to say a patient does not have an organic lesion. Radiologic examination renders valuable assistance in differentiating the conditions.

Treatment. Since the manifestations of visceroptosis are not always confined to the abdomen but are often protean in nature, it is necessary to recognize the general derangement from which the patient may be suffering if the treatment is to be successful. The treatment should be directed toward restoring the prolapsed organs to their normal position as far as possible, and to improve the general condition of the patient.

Patients with visceroptosis need an abdominal support, especially in the first few months of treatment. A large number of supports have been devised; some of them serve the purpose satisfactorily while many others are useless or harmful. The support should be fitted by a person who has both a knowledge of the anatomy of the abdomen and the object to be attained by the wearing of a support. It should be simply constructed of firm material, easily adjusted

and retained in position, and it should lift the lower abdomen. The support which accomplishes this purpose relieves the heavy dragging sensations in the abdomen by diminishing the tension on the mesentery and the intestines. It also relieves the backache. It is always well to see fluoroscopically if the support is holding the stomach and transverse colon in better position. Minor adjustments are often necessary. In the occasional patient when a well-fitting binder does not give the proper support, a change to another make will often have the desired effect. Many of the patients must continue wearing the support, while others may discard it in a few months, especially if they have gained weight and the tone of the abdominal muscles has increased under the influence of exercises and posture.

The orthopedic element of the treatment of visceroptosis consists in a process of reëducation of the individual that will lead to the assumption of a posture different from his habitual one. With a knowledge of body mechanics we can help him maintain the best and easiest posture that will strengthen the muscles. The assumption of the active posture will change the weight-bearing centers in the vertebral column to their normal position, and tension will be put upon the abdominal muscles. This will accomplish more in the treatment of ptosis than merely the prescribing of an abdominal support and corrective exercises. Corrective exercises, however, are indicated for increasing the expansion of the thorax and upper abdomen and at the same time increasing the tone of the abdominal muscles. They will also increase the strength of the spinal muscles.

In conjunction with the abdominal support and physical education, a few drugs are necessary for many of the patients. Dilute hydrochloric acid should be given to those who have a low acid secretion. Occasionally an alkaline powder will allay the sensitive gastric mucosa in the patients with a tendency to high acid secretion; and belladonna is indicated when any portion of the intestinal tract is irritable or spastic. Constipation should be overcome but purgatives should be avoided as far as possible. The bowels can be regulated usually by taking of mineral oil with the addition of agar if necessary. When constipation is not severe many patients will not require the oil except at intervals, after the first month or two of treatment. When constipation is intense, as it is in a number of these patients, we have found that small doses of aromatic cascara combined with iron and calcium lactophosphate will give excellent results. Later a combination of mineral oil and agar, or milk of magnesia will be sufficient. Ultimately, all laxatives should be omitted, if possible. Occasionally a mild sedative is necessary to quiet the irritable nervous system. Iron and arsenic are beneficial in stimulating the appetite in those patients who have little desire for food, and will also increase the erythrocytes and hemoglobin when an anemia is present.

A generous diet should be prescribed. It is a wiser policy for the patient to take four or five small meals during the day to avoid distending the stomach with large quantities of food. Cod-liver oil contributes splendidly toward upbuilding. As the weight increases, deposits of fat in the abdominal wall aid in supporting the viscera; the patient acquires a sense of well-being; and he is less easily fatigued.

Rest in the recumbent position is an important feature in the treatment. It relieves the tension on the mesentery and facilitates the movement of the gastrointestinal contents. The patient should lie down for thirty to forty-five minutes after each meal.

It is necessary that the patient continue the treatment. Even if, after a few months, the patient is able to do without the support and the drugs, he should continue the regimen of health-forming habits—correct posture, exercises, a rational diet, and rest. If he does not persist in carrying out these measures, the symptoms will recur.

Results of Treatment. It is interesting to observe the results of treatment in this series of cases. There was improvement in the gastrointestinal symptoms in all the patients though several of them complained of fullness and lassitude occasionally after meals. However, neither was as marked as before treatment. The dragging sensations in the abdomen with backache disappeared. The pain disappeared in 21 out of 26 patients, while in the remaining 5 it seemed to occur with an accumulation of gas and was referred to more as a dull aching sensation in the same region of the abdomen in which it formerly occurred.

In 10 of the patients with hypotension the systolic blood pressure increased from 4 to 22 mm. of mercury, and in 3 of those with postural hypotension the systolic pressure increased from 8 to 20 mm. There were variations in the systolic readings on subsequent observations of each patient. Some clinicians have reported that ephedrin increases the blood pressure. This drug was prescribed in 6 cases but we did not find that it raised the pressure above the level it had reached as a result of the treatment of the ptosis.

In 7 of the patients the nervous symptoms were prominent, and in all of them there was improvement although it was slower than the improvement noted in the other symptoms. Some of these patients complained of nervousness at irregular intervals but in only one was it as pronounced as before treatment. That patient, a man twenty-eight years of age, was susceptible to nicotine and he suffered from nervousness after smoking.

Coincident with improvement in the symptoms all of the patients gained weight, and experienced less mental and physical fatigue upon exertion. After a few months 12 patients discontinued treatment on account of feeling well. Their symptoms recurred but they improved quickly upon the reestablishment of treatment. Such

chronic infections as ethmoiditis, cervicitis and prostatitis were found in a few of the patients and were treated conservatively. Tonsillectomy was advised in 2 of 11 patients in whom infected tonsils were found.

Conclusions. 1. Roentgen ray studies of individuals have shown that there is a fairly constant relationship between the size, position and motility of the viscera and the body type. The two main types, the sthenic and asthenic with their subdivisions, the hypersthenic and the hypoasthenic, must be recognized, and the approximate normal level of the viscera in each type must be borne in mind before we can say that ptosis exists.

2. Visceroptosis is usually found in the asthenic person who has an inherent structural weakness; a faulty posture; relaxed muscles; and whose normal weight-bearing centers have shifted. There may be also an incomplete fusion of the right mesocolon or failure of the omental bursa to become obliterated. These defects are conducive to a downward displacement of the viscera. Ptosis occurs less frequently in the sthenic individual and is due to prolonged strain upon the abdominal muscles or to failure of the mesentery to develop properly.

3. Persons with ptosis may or may not have symptoms. They will develop symptoms when the intraabdominal pressure increases to a greater negativity, thus diminishing the peristaltic contractions in segments.

4. A study of the symptoms of 37 patients with ptosis shows that gastrointestinal symptoms are common to all, and that there may be symptoms referable to the circulatory system, especially when hypotension exists. A varying degree of disability was imposed upon the patients, especially upon those in whom hypotension was found. The sex incidence in this series is unusual in that males rather than females predominated.

5. This study shows that the symptoms of visceroptosis may simulate those of duodenal ulcer, chronic appendicitis and chronic cholecystitis. There are differences in the history that give a clue whether the symptoms are due to prolapse of the viscera or to organic disease. On physical examination we find certain characteristics that differentiate visceroptosis from other conditions. It is not difficult to determine the presence of ptosis, though it is sometimes difficult to say that organic disease does not exist. Roentgen ray examinations are valuable in the differentiation. Even when an Roentgen ray examination is not necessary it is desirable to have it made in order to determine the exact position of the stomach and colon.

6. Visceroptosis is not usually a disease, though it is often the cause of perverted physiology. Ptosis of one or more viscera in a sthenic person may be considered pathologic.

7. A diagnosis of enteroptosis, gastropptosis and coloptosis is justifiable as it denotes a certain anatomic topographic condition.

8. The treatment of visceroptosis should be directed toward returning the viscera to their normal position and improving the general condition of the patient.

REFERENCES.

1. Goldthwaite, J. E.: Orthopedic Principles in the Treatment of Abdominal Visceroptosis and Chronic Intestinal Stasis, *Surg., Gynec. and Obst.*, 1913, 16, 587.
2. White, J. R.: Visceroptosis in Relation to Posture, *Med. J. Australia*, (supp. 5), September 10, 1927, p. 133.
3. Mills, R. W.: Relation of Bodily Habitus to Visceral Forms, Tonus and Motility, *Am. J. Roentgenol.*, 1917, 9, 155.
4. Coffey, R. C.: The Principles Underlying the Surgical Treatment of Gastrointestinal Stasis Due to Causes Other than Structural or Uleerative Conditions, *Surg., Gynec. and Obst.*, 1912, 15, 365.
5. Waugh, G. E.: The Morbid Consequences of a Mobile Ascending Colon with a Record of 180 Operations, *British J. Surg.*, 1920, 7, 345.
6. Wagoner, G. W.: Studies on Intra-abdominal Pressure: Negative Intra-abdominal Pressure as a Normal Condition, *Am. J. Med. Sci.*, 1926, 171, 697.
7. Wagoner, G. W.: Studies on Intra-abdominal Pressure. II. The Effect of Variations of Intra-abdominal Pressure Upon Peristalsis of the Small Intestine, *abstr.*, personal communication.
8. Moody, R. O.: Are Diagnoses of Enteroptosis, Gastropptosis and Coloptosis Justifiable? *Am. J. Surg. (new series)*, 1929, 7, 470.

OBSERVATIONS ON VISCERAL PAIN.*

By R. D. RUDOLF,

PROFESSOR OF THERAPEUTICS, UNIVERSITY OF TORONTO; PHYSICIAN, DEPARTMENT OF THERAPEUTICS, TORONTO GENERAL HOSPITAL,

AND

A. G. SMITH,

RESEARCH FELLOW, DEPARTMENT OF THERAPEUTICS, UNIVERSITY OF TORONTO, TORONTO, CANADA.

PAIN in connection with visceral disease is an only too common complaint, and a large part of the practitioner's daily work consists in its diagnosis and treatment. What organ is at fault? What is the cause of the disturbance? Is the pain felt in the viscus under suspicion, or is it referred to superficial structures? Such questions are ever in his mind and the answers to them largely govern his conduct of the case.

At first glance it seems almost too evident for discussion that many pains are really felt in the organs in which the disturbance exists, and yet since the time of Haller, 1763, there have been many who have doubted this and say that there is no true visceral pain. Lennander¹ thought that all such pains were due to inflammation of, or pressure or traction on, the parietal peritoneum and its sub-

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serous layer, and therefore were somatic. Others believe that the pains are really referred from insensitive viscera and are felt in the parietal structures supplied by the cerebrospinal nerves which belong to the spinal segments to which the splanchnic nerves of the involved organs run. Such was the view of Sir James Mackenzie, who wrote, "Pains arising from the viscera are not felt in the organ, but are referred to the peripheral distribution of cerebrospinal nerves in the external body wall."³ Sir Henry Head endorses the referred nature of much pain in visceral disease, but adds, "I do not mean to state that pain is never felt in the organ affected. Far from it. The pain is frequently felt in the organ itself, but it is dull, heavy, wearing, and not sharp, aching, stabbing, like the referred pain."⁴

Those who do not believe in true visceral pain point to the fact that the viscera may be handled, burnt, pinched and in many ways physically insulted without much pain resulting. Recent work, however, has shown that this is only partially true. Thus C. H. Mayo wrote last year, "It can be shown that the structures in the abdomen are sensitive to pulling, clamping and tying."⁵ Hurst, who believes in visceral pain, says that the stimulus must be adequate, and that the only adequate stimulus is tension in the damaged organ. It is well known that the sensory nerve endings in the viscera are few in number, but they are present,¹⁶ and we must remember that although a normal tissue may have little sensation of pain, an inflamed one can be acutely sensitive. This point was emphasized by A. Primrose several years ago.⁷

Most will probably agree with Sir E. Farquhar Buzzard when he wrote, "Splanchnic pain is something very real, at any rate to anyone who has experienced the tortures of colic."⁹

But the question of whether or not true pain exists in a viscus is not the one in which we are especially interested here, but rather in the fact, admitted by most, that when some irritation occurs in an internal organ there is often pain with tenderness and muscular rigidity present in that part of the parietes which is innervated from the same spinal segment as receives the visceral nerves from the affected organ. This so-called "referred pain" may be only a slight part of the suffering which to the patient seems to be internal, or it may be the chief complaint and according to some the whole source of the distress. Ryle, who believes in the frequency of true visceral pain, thinks that when pain is referred it is usually evidence of inflammation of an organ. He concludes, "Non-inflammatory visceral pain, for example, intestinal colic, must be very severe before any somatic pain accompanies it."¹² In angina pectoris there is no inflammation of a viscus and yet terribly severe referred pain is often present.

It seems that some kinds of visceral irritation produce only referred pain and others apparently only true visceral pain, while in many both exist.

A common explanation of referred pain is that the afferent impulses from the irritated tissue on reaching the central nervous system spread to adjacent sensory centers and so excite these that painful impulses from them reach consciousness and are interpreted by the brain as coming from the peripheral distribution of such nerves. Thus when one has an inflamed tooth the pain may be felt not only in the tooth but also in the side of the face or in the ear. This is very clear when we are dealing with somatic nerves, but the same explanation is used when the afferent impulses must pass through the involuntary nerves and then spread and excite adjacent cerebrospinal cells. Thus in the case of irritation of the gall bladder pain may be felt in the parietes supplied by the eighth and ninth dorsal nerves; in angina pectoris in the distribution of the first to the fourth dorsal nerves, and so on. Such an explanation of the mechanism of referred pain is a very conceivable one anatomically when the whole course is somatic; and when the afferent portion is visceral we may recall the close connection which exists between the vegetative afferent nerves and the somatic, both in the posterior root ganglia¹⁵ and in the gray matter of the cord.¹⁶

But a difficulty arises, and it is with this difficulty that we are here concerned. If the superficial pain is referred, that is, if it is really due to excitation of the central cells and is only interpreted by the mistaken brain as coming from the peripheral distribution of that somatic neuron, any cutting or damaging of the nerves distal to the center should make no difference. The pain should still be felt as in the parietes, it only having been "projected there by the mind." (Lange.) But the experience of every physician as also of the laity is that when an anodyne application is made to an area of referred pain it tends to lessen it. Hilton had noted this and in 1863 wrote, "These superficial pains, although depending upon a remote cause, may sometimes be relieved by local anesthetics, as prussic acid, hemlock, belladonna and opium."¹⁷

In 1926 Lemaire published a paper¹⁸ on the relief of referred pain by infiltration of the skin with a solution of novocain, and two years later Weiss and Davis,¹⁹ working independently, showed that this acted very efficiently. Since then we have used the method in over 50 cases and our results fully confirm the fact that such pain and tenderness can usually be relieved by local anesthesia. We, like Weiss and Davis, usually used a 2 per cent solution of the drug.

And not only is the referred suffering relieved, but frequently what seems like true visceral pain may also be lessened. Case I is a good example of this. It is an interesting fact that referred pain is more easily got rid of than is true visceral pain. Several observers have noted that a whiff of chloroform may cause it to disappear while the original pain remains as before.

The following are a few examples from our series of cases. They are necessarily very briefly recorded, but it may be said that all

clinical methods were employed in the diagnosis, which in several instances was confirmed by operation.

Selection from Case Epitomes. CASE I.—Male, aged forty-five years. Diagnosis: Aneurysm of the arch of the aorta; syphilis. For the past six months suffered from pain in right chest. Would generally get some relief by local pressure or raising arm above head. Four months ago had to stop work on account of pain and since then has been confined to bed.

January 15, 1929. Is on Gatch frame and any movement in the bed causes pain. There is constant pain also over the third rib anteriorly about 3 inches from sternum.

Observation (a):

11.05 A.M. An area 3.5 by 3 cm. over painful region injected with 12 cc. of 2 per cent novocain intracutaneously.

11.10. The skin is anesthetic to touch.

11.15. Pain is distinctly less and area is not now tender to touch.

11.30. The dull aching in chest is lessening and moving about does not now aggravate it.

11.40. Pain is entirely gone. Patient can now move about without any discomfort.

11.55. Condition unchanged.

12.05 P.M. Pain is still absent.

1.10. Sensation is returning to skin. Pain still absent.

1.30. Pain is returning.

1.40. Pain is back as bad as ever.

Observation (b):

January 26, 1929. The same patient, complaining as before of pain made worse by any exertion. The pain is now chiefly along border of right scapula and there is some ache in right arm.

4.20 P.M. An area 3 by 1½ cm. along right border of scapula was infiltrated with 5 cc. of 2 per cent novocain.

4.25. The dull deep pain is subsiding.

4.27. Moving about or pressing back against chair does not cause pain as formerly.

4.35. Pain all gone from back. Still ache in right elbow.

4.50. Condition unchanged.

5.00. *In statu quo.*

5.20. No pain anywhere and is walking about comfortably.

5.30. Sensation of touch is returning. No pain.

5.55. Pain is returning.

6.30 Pain has returned in old situation beside border of scapula and deep in chest and is worse than before the injection.

NOTE.—Increase in severity of pain doubtless due to his increased activity while under the protection of novocain.

CASE II.—Female, aged fifty years. Diagnosis: Angina pectoris. Frequent attacks of severe pain in chest to right of sternum at the level of fourth rib. Also a tight feeling in upper chest that makes breathing difficult at times

Observation. October 20, 1929: The area of pain is very localized and is tender to touch.

8.30 P.M. An area 1 by 1½ inches was injected with 10 cc. of 1 per cent novocain.

8.40. Skin anesthetic to touch; pain is definitely less. Other sensations unchanged.

8.45. The acute pain is gone. There is still some soreness on deep pressure.

8.50. Patient completely relieved.

NOTE.—This patient stated that the relief was more speedy and more complete than with morphia.

CASE III.—Male, aged seventy-five years. Diagnosis: Chronic myocarditis and arteriosclerosis. For the last two weeks has had a pain at the angle of the left scapula of a dull aching character.

Observation. March 6, 1929:

2.30 P.M. An area 3.5 by 4 cm. was injected with 10 cc. of 2 per cent novocain.

2.40. Pain has gone and also tenderness.

2.50. Quite free from pain.

3.00. No change.

3.20. Resting quietly.

4.00. Resting quietly. Skin still anesthetic.

4.30. Sensation in skin returning.

5.00. Slight return of pain.

6.00. Pain has returned but not so bad as before.

NOTE.—Next day the pain was as bad as ever.

CASE IV.—Female, aged forty years. Diagnosis: Chronic heart disease and angina pectoris. Symptoms came on during pregnancy four years ago and cardiac reserve gradually lessened, and for last three months much dyspnoea and cyanosis, with cough and some blood-streaked sputum, and much pain.

Observation. February 17, 1929:

9 P.M. Complaining of much pain to left of sternum which is well localized. An area the size of a fifty-cent piece injected with 10 cc. of 2 per cent novocain. In a few minutes complete relief, and patient rested comfortably until 3 A.M.

NOTE.—Patient had often had morphia for her distress and stated that the novocain acted better and more quickly.

CASE V.—Female, aged thirty-eight years. Diagnosis: Cholecystitis. Has been troubled for the last month with flatulence and for the last twenty-four hours with severe pain in the region of the gall bladder which radiates around to the angle of the scapula. It is made worse by pressure and deep inspiration.

Observation. March 1, 1929:

11.55 A.M. An area of 9 sq. cm. over the gall bladder was injected with 20 cc. of 2 per cent novocain.

12.20 P.M. Pain is less over the gall bladder but is worse near the angle of the scapula.

12.25. Six square centimeters at angle of scapula were infiltrated with 16 cc. of 2 per cent novocain.

12.35. All pain gone.

12.50. Pain still absent.

1.00. No return of pain.

CASE VI.—Male, aged forty-seven years. Cholecystitis and duodenal ulcer. Was well until a week ago when he woke nauseated and dizzy, but did not vomit. Much pain in epigastrium, relieved by fluids until yesterday, when the pain became colicky and stabbing. Roentgen ray shows duodenal ulcer but no definite condition in gall bladder.

Observation. January 29, 1929:

5.15 P.M. Very severe pain over gall bladder which is aggravated by moving about and is tender to pressure. An area 4 by 3 cm. injected with 10 cc. of 2 per cent novocain.

5.20. The area is anesthetic to touch and the pain is beginning to fade away.

5.25. Pain is entirely gone and also the tenderness over gall bladder. Still same tenderness in epigastrium. Moving or sitting up does not now distress him. Before he could hardly bear being turned over.

5.30. Condition the same. When he moves quickly he gets a twinge of pain in right shoulder.

6.00. Sleeping.

NOTE.—Pain did not return when sensation did. Had a good night.

CASE VII.—Female, aged twenty-six years. Diagnosis: Cholecystitis. Patient took ill twenty-four hours ago when she was seized with severe pain in right upper abdomen and vomited. Diagnosis confirmed by Roentgen ray. Patient refused operation.

Observation: September 7, 1929: Pain is severe over gall bladder region. It is worse on moving and radiates through to the back.

3.40 P.M. An area of $1\frac{1}{2}$ by 1 inches infiltrated with 12 cc. of 2 per cent novocain.

3.50. Some relief. Pain not so sharp.

4.00. Pain has disappeared. Moving about still elicits some pain.

4.15. Quite comfortable.

5.00. Resting.

6.15. Pain is returning.

CASE VIII.—Female, aged twenty-one years. Diagnosis: Subacute appendicitis. Has had continuous pain and tenderness in right lower quadrant of abdomen for the last four days. The pain is aggravated by movement and by deep breathing.

Observation. February 20, 1929:

4.15 P.M. An area 3 by 2.5 cm. was marked off as the point of maximum pain and tenderness and 15 cc. of 2 per cent novocain was injected intradermically.

4.20. Pain is less severe.

4.30. Pain is gone. She can now move and take a deep breath without discomfort.

4.45. Pain is still away. Feels much relieved. Deep palpation elicits slight tenderness, but it requires more pressure than before.

5.00. Condition unchanged.

6.00. No pain over area injected. Slight pain over a new area lower down.

7.00. No pain. Still tender on deep palpation.

7.30. The same.

February 21. Pain returned in the early morning, but not so severe.

NOTE.—At operation the next day appendix found enlarged and club-shaped. Pathologic report was "acute appendicitis."

CASE IX.—Female, aged thirty-five years. Diagnosis: Carcinoma of the stomach, confirmed by Roentgen ray. For the past year or more has had pain in epigastrium with nausea and occasional vomiting. Pain radiates through to the back, and at the time of the treatment was in the left back just under the angle of the scapula.

Observation. August 21, 1929:

2.50 P.M. The painful spot, about 1 inch square, was infiltrated with 6 cc. of 2 per cent novocain.

2.55. Pain is less and hard to localize.

3.00. Pain has shifted to an area directly below the one injected.

3.05. The second area injected.

- 3.10. Pain has entirely gone.
- 3.20. Condition comfortable. No pain.
- 3.40. No change.
- 3.55. No change.
- 4.50. Pain is returning.

CASE X.—Female, aged twenty years. Diagnosis: Acute salpingitis. Has had profuse purulent vaginal discharge for over a year with pain in lower abdomen which is acute during menses, especially the last two. The pain is now localized to an area 2 by 2 inches above Poupart's ligament on the right side.

Observation. July 12, 1929:

12.15 P.M. Sixteen cubic centimeters of 2 per cent novocain used intracutaneously.

12.20. Area is anesthetic to touch and pain is less.

12.50. Pain now gone. Can move about comfortably. Deep pressure elicits some pain.

1.20. No pain. Sensation is absent.

2.00. Condition the same. Sensation to touch is returning. Patient vomited and had cold sweat.

2.20. Has occasional twinges of pain, but only slight.

3.30. No return of pain. Sensation completely returned.

8.00. Pain has returned with original severity.

July 13:

2.00. Pain in old area and 15 cc. of 2 per cent novocain injected.

3.00. Pain left her in ten minutes but tender on deep pressure.

NOTE.—The pain was similarly relieved on three succeeding days.

CASE XI.—Male, aged thirty-three years. Diagnosis: Spasm of the sigmoid flexure of the colon. For the last six months or so patient suffered from flatulence and occasional vomiting, with severe cramps in abdomen. At first had some diarrhoea without blood or mucus, but lately constipated and bowels moved only with enemata. Roentgen ray shows nothing except severe spasm of the sigmoid flexure which synchronizes with the paroxysms of pain.

Observation. The pain occurs rather indefinitely about the umbilicus and at times spreads around to back.

February 6, 1930:

4.30 P.M. Although the pain was hard to localize, it was more or less about the umbilicus, and an area 4.5 by 3 cm. on right side midway between the umbilicus and Poupart's ligament was infiltrated with 9 cc. of 2 per cent novocain.

4.35. Anesthesia, but no change in pain.

4.40. No change.

4.50. No change.

5.00. No change.

5.30. No change.

7.00. Sensation in skin has returned.

NOTE.—Possibly if a very large area had been infiltrated some relief might have resulted, but none came from what was done.

CASE XII.—Male, aged thirty-five years. Diagnosis: Ureteral colic. Was taken suddenly ill on December 15 with acute pain in the left flank. This came on while he was walking home from work and he only reached his house with difficulty. Laxatives and enemata were used without effect. There was some pain on passing water and the urine showed some pus and red blood cells, and the benzdinin test for blood was positive. No stone was visible in a flat Roentgen ray plate.

Observation. December 16, 1929: Severe pain in left flank just below the ribs.

3.55 P.M. An area $1\frac{1}{2}$ by 2 inches at site of pain was injected with 10 cc. of 2 per cent novocain.

4.00. Skin anesthetic to touch and pain is less severe.

4.10. Patient is resting quietly and is quite comfortable.

4.20. Pain is quite gone. There is tenderness on deep pressure lateral to the injected area. A second injection of 2 cc. relieved this considerably.

4.30. Patient is free from pain and is resting comfortably.

NOTE.—The pain did not return. Probably the novocain reflexly relieved the spasm of the ureter.

CASE XIII.—A healthy male volunteer swallowed a toy balloon attached to a rubber tube and pressure gauge. Under the Roentgen-ray screen the barium-treated balloon could be seen lying in the lower part of the esophagus. The pressure in the esophagus varied from 20 to 240 mm. of mercury, the latter during a spasm of vomiting.

After a period of rest the pressure in the balloon was slowly raised to 40 mm. Hg. and the subject felt definite pain over the lower part of the sternum. This area was quickly infiltrated with 5 cc. of 2 per cent novocain and soon the pain shifted lower down. The second area was injected and then the pain was in the epigastrium. This area was infiltrated and for two minutes there was no pain and then it appeared over the upper part of the sternum. A fourth injection was given and after this any increase in the pressure in the balloon caused no surface pain but a peculiar deep discomfort which could not be localized. There was no pain in the back at any time in the experiment.

NOTE.—This experiment was repeated on several volunteers with practically the same results.

The injections were done with a thin flexible needle intracutaneously so as to produce raised white wheals. Subcutaneous injection did not produce anesthesia, nor did relief occur if the injection was away from the painful area, showing that the results were not due to any systemic effect. Intracutaneous injection with normal saline produced some anesthesia and relief of pain, but the effects were only partial and very transient.

In many of the cases the pain was completely relieved by the injection; in some the superficial pain was lessened but a deep sense of discomfort remained; in several both superficial and deep pain disappeared. Where no definite superficial pain was present, but only deep suffering, as in intestinal colic, no relief was obtained by injecting over the surface. The very large area covered by such applications as fomentations and poultices may explain why these act.

In many instances the superficial pain was relieved but at once appeared lower down or to one side as was well shown in Case XIII. This condition, called *allocheiria*, is explained by the excitation spreading to adjacent centers in the central nervous system.

Discussion. These cases show that it is usually easy to relieve the referred part of visceral pain by local anesthesia, and also sometimes to dull to some extent what appears to be true visceral pain. While this fact is so evident most writers on the subject of referred

pain do not discuss its bearing on the nature of the phenomenon. Mackenzie, Head and Hurst do not mention it. Morley,² while giving many beautiful examples of the relief of the pain by local anesthesia, confines himself to the thesis that the pain is a peritoneo-cutaneous reflex phenomenon.

There have been however, several theories advanced as to how local anesthesia acts. Verger²⁰ suggests that the effect is due to an action on the theoretical connections in the skin between the cerebrospinal and sympathetic nerve endings. Sicard and Lightwiz²¹ believe that what they call "cutaneous shock" occurs, this shock sending up an inhibitory impulse which breaks the synapses between the sympathetic and cerebrospinal cells in the posterior root ganglia and especially in the cord. They put all forms of cutaneous therapy under the same heading and the action they believe is one of counterirritation. According to them intradermic infiltration with any nonacid solution acts as well as does novocain. As they put it, "intradermic injections appear in fact the modern method of using cutaneous therapy formerly so much employed in the form of cauteries, setons and blisters." Such counterirritation may account for some cases, but certainly in our experience normal saline injections do not relieve the pain nearly as well as does novocain and also it is hard to look upon gentle warmth as a form of counterirritation.

Lemaire¹⁸ insists that the novocain or other chemical anesthetic relieves pain by directly spreading up the nerves to the root ganglia as do the toxins of rabies and tetanus. Such a theory is hard to follow and certainly heat and cold cannot act in this way and yet often soothe pain efficiently. Weiss and Davis¹⁹ believe that the relief is due to the checking of the normal afferent impulses from the surface that are now, by reaching exciting centers, felt as pain, and hold that this supports Mackenzie's theory of referred pain. This theory of all pain in visceral disease was that the unfelt afferent impulses from the damaged viscus on reaching the cord spread to and excite neighboring cells including those of the cerebrospinal system. Normal afferent impulses now arriving from the surface are hence felt as pain.

While not for a moment agreeing that all pain from a viscus is felt in the parietes, our results suggest that an intact reflex arc, including the somatic portion, is essential for the appreciation of referred pain. The somatic neurons appear to require to be in a state of what might be called sensory tone or tension before they will respond to the afferent impulses coming from the irritated viscus or, indeed, from anywhere. A violin string will not vibrate in response to the irritation of the bow unless it be sufficiently tense and in an analogous way the cerebrospinal neuron must be in a state of tenseness or tone before referred pain occurs. Whether or not this tenseness is dependent upon the normal afferent impulses

from the periphery or upon some other fact or certain it is that numbing the terminations of the nerves stops the referred response to impulses coming from the region of the viscus. The somatic neuron is no longer intact.

Further, Weiss and Davis¹⁹ noted that "different types of sensation (pressure, heartburn, choking sensation, etc.) 'felt inside' were relieved by the infiltration of the skin," and everyone knows how such deep sensations are eased by soothing surface applications. They argue from this that these deep sensations are really referred to the parietes, but this, in our opinion, does not at all follow. We also noted that often deep discomfort was lessened by surface anesthesia but may not this be because the stopping of the parietal afferent impulses lessens the excitability of the visceral neurons, which now, having less tenseness, do not so easily respond to the messages coming from the irritated viscus? In the same way may be explained why surface numbing lessens various visceral reflexes and so eases colic and possibly visceral congestion. Adrian and Zotterman²³ have shown that the ascending impulses in a sensory nerve may vary from 7 to 100 per second, depending upon the intensity of the stimuli, and in proportion as these are lessened by surface anesthesia so will be the excitability of the centers. On the other hand, increasing the afferent impulses from the surface often increases deep pain, as seen when sudden chilling intensifies the pain of angina and may induce colic.

Lastly it is evident that in referred pain the suffering may be lessened by an attack on either end of the viscero-sensory reflex arc. Thus, the referred pain in angina pectoris can be diminished by anesthetizing the painful area on the surface or more specifically by relieving the tension in the heart or aorta by lowering the blood pressure; the surface pain in biliary colic may be wiped out by infiltrating the skin or by relaxing the biliary passages by benzyl benzoate; that of duodenal ulcer by anesthetizing the skin or by the administration of alkalies, and so on.

Conclusions. 1. True visceral pain exists. It is usually dull but may be very acute.

2. Such visceral pain may occur alone or be accompanied by referred pain which will appear in the distribution of the somatic nerves that come from the segment of the central nervous system with which the affected visceral nerves are connected.

3. In many instances the referred pain is the only one that reaches the level of consciousness.

4. Referred pain is more easily relieved than is that coming from the source of the irritation. This relief can be obtained by the use of various anodyne applications and especially by the infiltration of the skin by anesthetics, such as novocain.

5. Often such anodynes will also, to a certain extent, relieve the deep suffering, but sometimes this is not the case and the afferent

impulses from the source of irritation may, without any amplification from the periphery, be sufficient to reach the sensorium.

6. When a referred pain is present it may be relieved either by attacking it at its distribution or, more specifically, by directly treating the cause of the irritation.

7. The theory advanced here is that for referred pain to occur it is essential that the whole sensory reflex arc be intact.

BIBLIOGRAPHY.

1. Lennander, K. G.: *J. Am. Med. Assn.*, 1907, **49**, 836.
2. Morley, John: *Lancet*, 1929, ii, 1240.
3. Mackenzie, Sir James: *Symptoms and Their Interpretation*, 1909, p. 51.
4. Head, Sir Henry: *Brain*, 1893, **16**, 126.
5. Mayo, C. H.: *British Med. J.*, 1929, ii, 703.
6. Hurst, A. T.: *The Sensibility of the Alimentary Canal*, 1911, p. 47.
7. Primrose, A.: *Canadian Med. Assn. J.*, 1924, **16**, 826.
8. Brown, Langdon: *The Sympathetic Nervous System in Disease*, 1923, p. 16.
9. Buzzard, Sir E. Farquhar: *British Med. J.*, 1929, ii, 705.
10. Hunter, John I.: *Med. J. Australia*, 1920, ii, 115, 143.
11. Kinsella, V. J.: *Lancet*, 1926, i, 1131.
12. Ryle, A. J.: *Lancet*, 1926, i, 895.
13. Head, Sir Henry: *British Med. J.*, 1922, i, 4.
14. Ross, J.: *Brain*, 1888, **10**, 350.
15. Edinger, Ludwig: *Bau der nervösen Zentralorgane*, 1908.
16. Pottenger, F. M.: *The Symptoms of Visceral Disease*, 1925, p. 77.
17. Hilton, John: *Rest and Pain*, 1879, p. 149.
18. Lemaire: *Bull. Acad. de méd. de Belgique*, 1926, Series V, Tom. 6, 158, 307.
19. Weiss, S., and Davis, D.: *AM. J. MED. SCI.*, 1928, **176**, 517.
20. Verger: *Gaz. hebdomadaire des Sciences méd. de Bordeaux*, 1927, **1**, 27.
21. Sicard, J. A., and Lightwitz, A. N.: *La presse méd.*, 1929, **37**, 545.
22. Poulton, E. P.: *Lancet*, 1929, ii, 1223.
23. Adrian, E. D., and Zotterman, Y.: *J. Physiol.*, 1926, **61**, 151.

REVIEWS.

AFFECTIONS OF THE EYE IN GENERAL PRACTICE. By R. LINDSAY REA, B.Sc., M.D., M.Ch., F.R.C.S. Pp. 155; 40 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$3.50.

THIS small book is written primarily to assist the general practitioner in the diagnosis and treatment of the more common diseases of the eye. The author expresses himself in a clear and concise manner, and covers the ground adequately. He also stresses certain cases that should be referred to the specialist. There are sixteen chapters in the book. The first seven deal with the diseases of the various anatomical structures of the eye, beginning with the lids and working backward. There are also chapters on glaucoma, errors of refraction, squint, injuries to the eye, cataract, the examination of the eye in diseases of the nervous system, localizing value of eye symptoms in the diagnosis of diseases of the brain, the orbit, and the hygiene of the eyes. A list of therapeutic formulæ and an adequate index conclude the volume.

The author is to be congratulated on covering the ground in such a concise and practical manner. This book would be an asset to any general practitioner's library.

A. F.

ANNALS OF ROENTGENOLOGY, VOL. XI. THE CHEST. By L. R. SANTE, M.D., F.A.C.P., F.A.C.R., Edited by JAMES T. CASE, M.D. Pp. 561; 246 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$20.00.

THE author has admirably accomplished his purpose as stated in the preface, namely, that this volume was undertaken "for the aid of the clinician and to serve as a compilation for the guidance of roentgenologists." He has attempted to lay down the broad general principles of roentgenology of the chest, avoiding detailed discussion of individual subjects. The volume is, therefore, a distinct addition to reference works on roentgenology. It will serve as a firm foundation for the beginner and as an excellent guide to the experienced roentgenologist.

The plan of presentation of the subject is very good. Due consideration is given to the technique of roentgenologic examinations, the Roentgen anatomy of the chest, the physiology of respiration and the principles of roentgenologic interpretation. Of special merit is that portion of the book devoted to roentgenologic evidences of disease. Here numerous diagrams are used to illustrate the various types of pathologic processes to be encountered in the lungs. The major portion of the volume is devoted to the roentgenologic characteristics of individual diseases. The work is profusely illustrated by diagrams and reproductions of roentgenograms. These are accompanied by rather full and concisely stated explanatory notes.

While this book will be primarily of interest to roentgenologists, there is much that the clinician will find of interest and value in its contents.

K. K.

CLIO MEDICA, VOL. I. THE BEGINNINGS—EGYPT AND ASSYRIA.
By WARREN R. DAWSON, F.R.S.E. Pp. 86. New York: Paul
B. Hoeber, Inc., 1930. Price, \$1.50.

THIS interesting book auspiciously inaugurates "Clio Medica," a series of conveniently small, inexpensive but invaluable volumes that present in a concise and pleasantly readable form certain aspects of the long, complex but fascinating history of the origin and development of the medical sciences. The author of this first volume of the series is a distinguished authority in all matters of ancient medical lore.

His contributions concerning medical history, many and valuable, are, fortunately, based upon direct and prolonged study of the earliest medical inscriptions, papyri and manuscripts and not upon opinions derived from reading.

It has been well and truly said that a science or an art is best understood when its origins are known.

The author turns back the pages of time to the very beginnings of written medical history in an authoritative but pleasing style and makes the reader aware of the exact truth of Charcot's statement that "disease is of old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible."

The book is an excellent antidote for egoism and complacency, traits inexcusable in a member of the medical profession, for it clearly reveals that our advance in knowledge and vision is a result of our being able "to stand upon the shoulders of those of our profession who paved the way for us." If all the volumes of "Clio Medica" prove as instructive and thought-productive as "The Beginnings" the entire medical profession will owe a debt of gratitude to the Editor.

E. B.

ENDOCRINE DISORDERS. By PROF. HANS CURSCHMANN. Pp. 188; 46 illustrations. London: Oxford University Press, 1929. Price, \$4.00.

IN a field where so much has been claimed on too little evidence, it is a pleasure to read this conservative, evenly balanced little book. It is well written, concise but adequate, and should be of particular value to the practitioner and the medical student. Illustrations are numerous and well chosen. Quite up to date at the time of publication, yet it dismissed with a paragraph, as "purely speculative," human hyperparathyroidism, established within a few months as a clinical entity.

R. K.

THE COMMON HEAD COLD AND ITS COMPLICATIONS. By WALTER A. WELLS, A.M., M.D., F.A.C.S. Pp. 225; 15 illustrations. New York: The Macmillan Company, 1929. Price, \$2.75.

THE author states as the object of this book the presentation to the layman of "the best and most recent knowledge of the profession on the subject of the origin and nature of the common cold and its complications—why we catch them, how we can avoid them and what we can do to get rid of them." This he has succeeded in doing very well and the reader will find the work adequate, well expressed, interesting and accurate. The Reviewer is, however, a bit puzzled over what purpose might be served in a book for laymen by an illustration of the author's method of vessel ligation in tonsillectomy.

R. K.

OUTLINE OF PREVENTIVE MEDICINE.. By twenty-one contributors. Pp. 398. New York: Paul B. Hoeber, Inc., 1929. Price, \$5.00.

MOST works on preventive medicine have presented the subject from the standpoint of the specialist in public health, hygiene and sanitation. This book, on the contrary, is written expressly for medical practitioners and students, with the purpose of emphasizing preventive measures as applicable in general practice. A group of eminently qualified writers have contributed chapters on such subjects as the Periodic Health Examination; General Medicine; the Surgical Aspects; preventive medicine in the specialties: Allergy, Tuberculosis, Orthopedics, Obstetrics, Gynecology, Pediatrics, Nervous and Mental Disease, Dermatology, Urology, Venereal Diseases, Diseases of the Eye, Ear, Nose and Throat, Industrial and Occupational Diseases, etc. The various fields have been adequately and well presented. The chapters on the general medical and the surgical aspects are, however, too short, with more emphasis on early

diagnosis than on original prophylaxis. There is some unnecessary duplication (for example, asthma, tetanus, diphtheria, syphilis, rabies, etc.). Three pages are devoted to typhoid fever, but only three lines to undulant fever of bovine origin. These are, however, minor defects; the book really represents a valuable contribution to this important field and is to be recommended highly to practitioners and students. The volume itself is a very creditable product of the bookmaker's art.

R. K.

DISEASE AND THE MAN. By GEORGE DRAPER, M.D. Pp. 270; 52 illustrations. New York: The Macmillan Company, 1930. Price, \$4.50.

IN this volume are set forth the author's further studies since the publication in 1924 of his book, *Human Constitution*. The argument: If persons with certain disease tendencies are subjected to analysis of their morphology, physiology, psychology and immunology, there is found a high degree of correlation between these phases of the individual, so that knowledge of one phase makes it possible to predicate, at times with surprising accuracy, the characters constituting one or more of the others. The part played by heredity, modified by environmental factors, in determining the individual's constitution is discussed in the chapter on Genetics. Under Morphology are described methods of anthropometry and findings in a number of disease groups. There follow chapters on The Influence of Sex, on The Psychologic Panel, a Clinic for the Presentation of Constitutional Type (as given by the author before senior medical students) and a closing chapter: The Patient and His Physician (originally written as a lecture for laymen, even more valuable to physicians). The whole subject is most important and as the author, a pioneer in the field, presents it, one of great interest and fascination. Physicians and medical students will find this book instructive and delightful reading.

R. K.

WHAT EVERYONE OUGHT TO KNOW. By OLIVER T. OSBORNE, M.D. Pp. 313. Springfield, Ill.: Charles C. Thomas, 1929. Price, \$2.50.

APPLIED physiology and hygiene for popular consumption. The author's book contains a surprising amount of information; the advice is sane, sound and is wholly untainted with the "fad" tendencies so common among those who undertake to tell us how to regulate our lives and bodies. In fact, the Reviewer would find nothing with which violently to disagree (he was delighted with the chapters on Nutrition, Foods, Diet and Promotion of Health; a bit

surprised at the alleged villainous character of the bristle tooth brush and at the omission of the alcohol question; he is sure that the statement, "It is the iron constituent of the blood that changes the carbon dioxide to oxygen" was unintentional). The style is chatty, occasionally a bit garrulous and tautologic, but always interesting. Physicians may well recommend this excellent book to their families and patients. R. K.

REPORT ON MUSSEL PURIFICATION. By R. W. DODGSON, M.D. (LOND.), M.R.C.P. (LOND.), M.R.C.S. (ENG.). Pp. 498; 65 illustrations. London: His Majesty's Stationery Office, 1928. Price, £1, 1s.

THIS exhaustive study deals primarily with the subject of mussels, but much of the data is applicable also to shellfish in general and to oysters in particular.

The principal topics considered are: pathologic conditions which may follow the consumption of mussels (typhoid, mussel poisoning and the like); the pollution of shellfish beds, together with methods of detection, prevention and palliation; the physiology of mussels and experimental and practical methods of purifying them when polluted; tests to determine the efficiency of purification; bacteriologic methods and standards of purity.

The book is well printed on a good grade of paper, and is serviceably bound. The illustrations are excellently done and instructive. There are 126 bibliographic references.

The principal use for this work will be in the hands of public health workers and those concerned with the cultivation of shellfish.

F. L.

THE BACTERIOPHAGE AND ITS CLINICAL APPLICATIONS. By F. D'HERELLE, Professor of Bacteriology. Pp. 254. Springfield, Ill.: Charles C. Thomas, 1930. Price, \$4.00.

THIS book is well printed, on a good quality of paper, and is serviceably bound.

The subject matter is divided into seven chapters, dealing respectively with Bacteriophagy, Bacterial Mutations, Nature of Bacteriophage, Infectious Disease, Recovery and Immunity, The Use of Bacteriophage, and Conclusions.

These sections cover the essentials necessary to an understanding of the development and mechanism of bacteriophagy.

The material is logically and interestingly presented, in a style which can be readily followed, although the author states his views with such finality that one cannot help feeling he attaches too little

weight to conclusions of other workers who also have contributed to our knowledge of this important subject.

Since this book is intended primarily for physicians, there is too little space devoted to the methods of preparation of bacteriophage filtrates and the details of their therapeutic use. It seems to the Reviewer that it would be well if there were more discussion of the type of cases in which bacteriophage therapy is unsuccessful, and, if possible, the reasons for the failures reported by other observers, and suggestions for overcoming them.

F. L.

INCOMPATIBILITY IN PRESCRIPTIONS AND HOW TO AVOID IT. By THOMAS STEPHENSON, D.Sc., Ph.C., F.R.S. (Edin.); F.C.S. Pp. 61. New York: Paul B. Hoeber, Inc., 1929. Price, \$1.50.

A CONCISE statement of the general principles underlying incompatibilities, following an outline form, with numerous examples and a list of incompatibilities according to drugs, alphabetically arranged. A valuable book, it would have been made still more so if it had been made up in a handy pocket size.

R. K.

ALIMENTARY ANAPHYLAXIS. By GUY LAROCHE, CHARLES RICHEL FILS and FRANCOIS SAINT-GIRONS, Paris, France. Forward by PROF. CHARLES RICHEL of the Faculty of Medicine of Paris; translated by MILDRED P. ROWE and ALBERT H. ROWE, M.D. Preface by ALBERT H. ROWE, M.D. Pp. 139. Berkeley: University of California Press, 1930. Price, \$2.00.

WRITTEN in 1919 by three French physicians who theorized rather far on the basis of their clinical observations, this little book on food allergy has found much confirmation in the intervening years. It will be of interest to those engaged in this special field. The translation is excellent.

R. K.

BOOKS RECEIVED.

NEW BOOKS.

The Surgical Clinics of North America, Vol. 10, No. 4 (Southern Number, August, 1930). Pp. 268; 96 illustrations. Philadelphia: W. B. Saunders Company, 1930.

Medical and Surgical Year Book, Physicians Hospital of Plattsburgh, Vol. 1, 1929. Pp. 322; illustrated. Plattsburgh: The William H. Miner Foundation, 1930.

* Reviews of titles followed by an asterisk will appear in a later number.

- Dietetics and Nutrition*.* By MAUDE A. PERRY, B.S. Pp. 332. St. Louis: The C. V. Mosby Company, 1930. Price, \$2.50.
- Krankheiten und Hygiene der Warmen Länder*.* By PROF. DR. REINHOLD RUGE, PROF. DR. MÜHLENS, and PROF. DR. MAX ZUR VERTH. Pp. 494; 496 illustrations. Verlag, Leipzig: Georg Thieme, 1930. Price, M. 39.60.
- Heat Pyrexia. No Heat Stroke. No Heat Fever*. By C. J. McCARTIE: M.A., M.D., M.Ch., Lt-Col., I. M. S. (retired). Pp. 27. Dublin, Browne & Nolan, 1930. Price, 1/-.
- Recent Advances in Chemotherapy*.* By G. M. FINDLAY, O.B.E., M.D., D.Sc., with a Foreword by C. M. WENYON, C.M.G., C.B.E., M.B., B.S., B.Sc., F.R.S. Pp. 532; 15 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1930. Price, \$3.50.
- The Physiology of the Vestibular Apparatus*.* By MARIO CAMIS; translated and annotated by R. S. CREED, B.M., B.Ch., M.A. Pp. 310; 65 illustrations. New York: Oxford University Press, 1930. Price, \$7.50.
- Tropical Medicine in the United States*.* By ALFRED C. REED, M.D. Pp. 410; 60 illustrations. Philadelphia: J. B. Lippincott Company, 1930. Price, \$6.00.
- A Compilation of Culture Media*.* By MAX LEVINE, Ph.D., and H. W. SCHOENLEIN, M.S. Pp. 969. Baltimore: The Williams & Wilkins Company, 1930. Price, \$15.00.
- Handbook of the Vaccine Treatment of Chronic Rheumatic Diseases*.* By H. WARREN CROWE, D.M., B.Ch. (Oxon.), M.R.C.S., L.R.C.P. Pp. 52. New York: Oxford University Press, 1930. Price, 80¢.
- Elements of Psychology for Nurses*.* By REV. JAMES FRANCIS BARRETT. Pp. 326; 8 illustrations. Milwaukee: The Bruce Publishing Company, 1930. Price, \$2.50.
- Feeding in Infancy and Childhood*.* By I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D. Pp. 345; 37 illustrations. Philadelphia: J. B. Lippincott Company, 1930. Price, \$6.00.
- Burns—Types, Pathology and Management*.* By GEORGE T. PACK, B.S. M.D., and A. HOBSON DAVIS, B.S., M.D. Pp. 364; 60 illustrations. Philadelphia: J. B. Lippincott Company, 1930. Price, \$6.00.
- Chronic Nasal Sinusitis*.* By PATRICK WATSON-WILLIAMS. Pp. 221; 110 illustrations. New York: William Wood & Co., 1930. Price, \$5.00.

NEW EDITIONS.

- Injuries to Joints*.* By SIR ROBERT JONES, BART., K.B.E., C.B. Pp. 195; 29 illustrations. Third edition. New York: Oxford University Press, 1930. Price, \$2.00.
- Manual of Physiology*.* By H. WILLOUGHBY LYLE, M.D., B.S. (Lond.), F.R.C.S. (Eng.), and DAVID DE SOUZA, M.D., D.Sc. (Lond.), F.R.C.P. (Lond.). Pp. 820; 138 illustrations. Third edition. New York: Oxford University Press, 1930. Price, \$5.25.
- A System of Clinical Medicine*.* By THOMAS DIXON SAVILL, M.C. (Lond.). Pp. 1019; 167 illustrations. Eighth edition. New York: William Wood & Co., 1930. Price, \$10.00.
- Personal and Community Health*.* By CLAIR ELSMERE TURNER, M.A., Dr. P.H. Pp. 443; 62 illustrations. Third edition. St. Louis: The C. V. Mosby Company, 1930.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Immunity of Certain Anatomic Regions From Lesions of Skin Leprosy.—Leprosy is by no means an easy disease to diagnose. Under certain conditions the typical case may be recognized by the tyro. On the other hand, men with extensive experience with the disease are often at a loss to know if the patient does not or does have the disease. HOPKINS, DENNEY and JOHANSEN (*Arch. Dermat. and Syph.*, 1929, 20, 767) have studied the location of the lesions of leprosy in 302 patients, 245 of whom had typical leprous skin lesions. They write that certain areas of the body are conspicuous as a result of their exemption from the involvement of the leprous lesion. This is certainly a diagnostic observation of considerable importance. The areas in which macules, infiltrated patches and nodules of leprosy practically never occurred are those sites which are least exposed to irritation from such sources as sunlight, heat, cold, pressure, friction and other stimuli likely to produce local hyperemia. The posterior inferior auricular area, the cavum conchæ, the orbital surface of the nose, the lateral palpebral area, the axilla, the inframammary fold in women, the interdigital surface and the perineum were exempt from lesions in all cases. The scalp, mesolabial fold and the sulcus of the upper eyelid were involved in only 2, 4 and 2 instances. The authors suggest that in these areas mentioned conditions are not favorable to the growth of the bacillus of Hansen.

Recoveries from Leprosy.—AN ANALYSIS OF THE RECORDS OF 65 CASES.—DENNEY, HOPKINS and JOHANSEN (*Pub. Health Rep.*, 1930, 45, 667) report on 65 patients who have been admitted to the National Leper Home at Carville with leprosy and who have been discharged from that institution as cured. They make a note in their paper that between the time of the presentation of this report and January 23,

1930, 8 additional lepers were paroled. This makes a total series of 73 patients who have been observed in the last ten years in whom there have been something under 3 per cent of relapses. This is a very remarkable record, indeed, and it discounts clearly the idea held from time immemorial that leprosy is incurable. Some of these patients had been in the leprasorium for many years. Some of them had no sequelæ of leprosy when they were discharged and few of them had marked leprous sequelæ, such as total blindness, loss of all phalanges and similar leprous lesions. The majority of these patients received chaulmoogra oil; 55 received a crude oil; 12 received intramuscular injections of benzocain-chaulmoogra oil; 21 received ethyl esters of chaulmoogra oil by intramuscular injection. It should be appreciated that in this group of patients many received several forms of treatment. In addition to those who may have received chaulmoogra oil by mouth as well as by injections, there are some who were given mercurochrome intravenously, several who took Fowler's solution and several who were given salvarsan. In addition to the chaulmoogra oil and more or less specific treatment, certain hygienic, physiotherapeutic and psychotherapeutic measures were also employed in the treatment of these patients. Of these 65 patients whose clinical history is detailed in the report, 12 were of the nodular type of leprosy, who remained in the hospital on an average of five and four-fifth years. Twenty-six of the patients were of the mixed type, hospitalized for an average of five and a half years, and 27 of the paroled cases were of the anesthetic type with an average period of hospitalization of nine years. This splendid record of cures must be of tremendous interest to the leper himself. One of the features of the disease that has to be combated most consistently is the tremendous mental depression under which the patients labor. Knowledge of the increased tendency to cure the disease should certainly greatly enhance the possibility of ultimate recovery.

The Circulatory Failure of Diphtheria. III. The Treatment of the Circulatory Failure of Diphtheria.—In an earlier communication SCHWENTKER and NOEL discussed the evidence which indicated to them that circulatory failures in diphtheria may be of two types: an early failure occurring as a part of a general toxemia, and late failure probably due to inflammatory reactions in the heart and conduction system developing during the process of regeneration and repair. They (Schwentker and Noel, *Bull. Johns Hopkins Hosp.*, 1930, 46, 359) now write that: as the mechanism of production of the two types of circulatory failure differ so essentially, it correspondingly follows that the treatment of the two types of failure should be entirely different. In the acute, early failures because of the disturbance of carbohydrate metabolism that occurs in diphtheria poisoning, glucose should be given in large quantities at frequent intervals and guarded by insulin. Specifically, the general management of such cases includes a preliminary dose of antitoxin, mentioned in the article as being "large." If no reaction has taken place a half an hour later, 10,000 to 20,000 units of antitoxin plus 20 gm. of a 50 per cent solution of dextrose are given,

10 to 20 units of insulin being given with the dextrose. At intervals from ten to twenty-four hours, the intravenous injection of dextrose is repeated, always being supplemented by insulin, a unit of insulin for each 1 to 2 gm. of dextrose. After the first two injections a 10 per cent solution of dextrose is given in order to get the beneficial effects of the additional fluid. In the 14 patients that they treated in this manner, all of whom appeared close to death, several of whom were unconscious when first seen, 13 survived.

Experimental Epidemiology of Tuberculosis. The Effect of Crowding Upon Tuberculosis in Guinea Pigs, Acquired by Contact and by Inoculation.—LURIE (*J. Exper. Med.*, 1930, 51, 729) writes that there has been some question as to whether or not normal guinea pigs in the same room but not in the same cage with tuberculous animals may acquire the disease. In order to reinvestigate the question he exposed 103 guinea pigs who apparently were nontuberculous in the same room with a series of animals that had the disease. Fifteen of these pigs, or 14.5 per cent, developed tuberculosis after a long period of exposure, the shortest time in which tuberculosis developed being eight months. Most of the guinea pigs were exposed for thirty-two months without becoming tuberculous. The possibility arises that this freedom from the disease may be due to a natural resistance to tuberculosis or to an acquired immunity developed after long-continued exposure. The animals that died evinced a characteristic chronic type of the disease. There was marked involvement of the lungs, frequently cavity formation, extensive tuberculosis in the tracheobronchial lymph nodes, while the cervical and mesentery glands were but slightly affected.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Bone-block Operation for Dropfoot: Analysis of End Results.—CAMPBELL (*J. Bone and Joint Surg.*, 1930, 12, 317) claim that that the object of the method is to construct an osseous process posterior to the ankle joint, which is attached to the os calcis and which will impinge upon the articular surface and the posterior surface of the tibia, blocking ankle motion at about 10 degrees of plantar flexion. The operation is simple, as the bone for transplantation is usually available from associated operative procedures. Apparatus may be discarded as a natural internal brace is constructed. Muscle power is conserved by overcoming the constant force of gravity. Prevention of overstretching may of itself permit a return of dormant muscle power. Rocker

motion of the ankle joint is conserved. Stabilization is rendered more effective by the bone block and incident additional fusion induced between the astragalus and the os calcis. The percentage of satisfactory and permanent end results in the stabilization of paralytic feet has been found to be thus materially increased.

Goitrous Enlargement of the Thyroid Gland Due to Amyloidosis.—HUNTER and SEABROOK (*Arch. Surg.*, 1930, 20, 762) state that a reported instance of advanced amyloidosis of the thyroid gland, producing enlargement of the gland and symptoms of pressure stenosis of the trachea, is chronic pulmonary tuberculosis. It is the most common cause of amyloid formation and adequately explains its presence in this case. The results of the Congo-red absorption test indicates that the patient did not have a widespread amyloidosis. The present study confirms the observation of previous investigators that in the thyroid gland amyloid substance is deposited chiefly in the vascular interalveolar spaces. Amyloidosis of the thyroid gland is seldom encountered in surgical practice. The nature of the process may be suspected or diagnosed at operation by the bacon-like or fatty appearance of the gland and distinguished from a malignant process by the almost complete lack of hemorrhage during the course of the operation.

Carcinoma of the Small Bowel.—RANKIN and MAYO (*Surg., Gynec. and Obst.*, 1930, 1, 939) refer to the cases of carcinomata and sarcomata reported in the literature, but base their study on the carcinomata of the small bowel appearing in The Mayo Clinic from and including the year 1919, Judd having reported on the cases before that year. Between January 1, 1919, and October 1, 1929, inclusive, carcinoma occurred in the small bowel 31 times as compared with 2775 times in the large bowel and rectum and 2646 times in the stomach. Adding Judd's cases, reported in 1919, there have been 55 cases of carcinoma of the small intestine compared with 4597 of the large bowel and rectum together, and 4335 of the stomach. It represents, at The Mayo Clinic, 0.062 per cent of the cases of carcinoma of the gastrointestinal tract. The primary signs and symptoms are directly relative to intermittent obstruction and to secondary anemia. Duration of symptoms varies with the individual case, but the average is fourteen to fifteen months. A movable tender mass that "slips away from the fingers" should arouse suspicion. The tendency, as noted in the history, is for constipation to be a rather constant symptom and for it to become increasingly obstinate, although occasionally it is interspersed with attacks of diarrhea. Repeated tests for occult blood are important in suspicious cases. Roentgenologic examination is of particular importance only from a negative standpoint in the present state of knowledge, but it seems likely that future progress along diagnostic lines will make the roentgenologic examination much more accurate and definite. Resection and end-to-end anastomosis is the surgical procedure of choice. When this is not possible lateral enteroanastomosis should be done to short-circuit the obstruction. The prognosis is poor regardless of the procedure. Metastasis takes place early.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

Investigations on the Action of Novasurol on Trichinosis in Rats.—Citing the very favorable results in the treatment of 2 cases of trichinosis in man reported by Jochweds and Pekieli, CHÜKRI (*Klin. Wchnschr.* 1930, 9, 298) made a series of carefully controlled studies on the action of novasurol on trichinosis in rats, from which he finds that novasurol exerts no inhibitory or destructive action on the intestinal, blood or intramuscular trichina. Furthermore there is no apparent influence on the course of the disease in rats caused by the injection of novasurol.

The Use of Emetin in Nonamebic Abscesses of the Lung.—Evidence is available in the literature that emetin is a useful therapeutic agent in a number of other conditions besides amebiasis. Its use is advocated in certain cases of acute and chronic bronchitis, in spirochetosis of the lungs, and in cases of pulmonary hemorrhage. NUBERT and BRANIS-TEANU (*Presse méd.*, 1930, 9, 132) have used emetin hydrochlorid with beneficial effect in 2 cases of nonamebic pulmonary abscesses and in 4 cases of purulent non-"fuso-spirochitic bronchitis." In one of the patients with pulmonary abscess daily subcutaneous injections of 0.04 gm. of emetin hydrochlorid resulted in prompt decrease of the fetid expectoration. In about seventeen days the patient felt well and Roentgen ray examination showed that the shadow due to the abscess had disappeared. In the other cases, repeated injections of doses of 0.02 and 0.04 gm. caused the disappearance of the purulent nature of the expectoration but the objective evidence of the pulmonary pathology persisted. The authors claim that in purulent bronchitis emetin is a useful drug; it causes a decrease in the amount of the secretion and the disappearance of the fetid odor of the sputum. It also causes improvement in the general condition of the patient.

Endonasal Application of Insulin.—WASSERMEYER and SCHAEFER (*Med. Klin.*, 1930, 26, 474) report the results of investigations designed to determine whether or not a satisfactory method for administering insulin intranasally could be developed. They employed in their tests both normal persons and those suffering from the milder forms of diabetes. To these, under well-controlled conditions, they administered insulin intranasally in the form of powders, as well as in solution, and in doses varying between 10 and 100 units. Control observations were

made with the administration of the same preparation of insulin by the usual subcutaneous method. Among the preparations studied were dried insulin powder mixed with sodium borate, with saponin, caffein, theocin and primary phosphates. They also employed a mixture of insulin with desoxycholic acid. Of these the most effective and the least objectionable was the mixture with sodium borate. That with desoxycholic acid proved irritant and was very objectionable in taste. That with saponin was very irritant, while the remaining mixtures exerted no insulin action. Simple solutions of insulin in water or in physiologic saline were administered in the form of sprays and also by means of cotton tampons saturated with the solution. With these solutions applied by either method and with the powder containing sodium borate they observed in both normal and mildly diabetic persons inconstant and only mild reductions in the blood sugar together with the frequent reappearance of sugar in the urine shortly after the administration. They found further that no greater effects were produced by doses of 50 to 100 units than were obtained in the same persons from doses of 10 to 20 units. Efforts were made to determine the reason for the frequent ineffectiveness of nasal administration and the reason for the failure of large doses to be more effective than small ones, but these efforts yielded no satisfactory explanation. The authors conclude that the endonasal administration of insulin may be of slight value in mild cases of diabetes, but that it is not of sufficient trustworthiness to warrant its recommendation.

The Treatment of Carbon Monoxid Poisoning by Ultraviolet Irradiation.—Acting upon the observations of Haldane and of Hartridge, which show that the dissociation of CO hemoglobin is markedly increased under the influence of the ultraviolet light, Koza (*Med. Klin.*, 1930, 26, 422) declares that a similar increase in the elimination of CO can be produced in animals poisoned thereby. In a series of experiments in which the usual methods for resuscitation were employed, including the administration of oxygen, carbon dioxid and respiratory stimulants, those animals which were also exposed to the ultraviolet rays of a quartz lamp showed considerably more rapid recovery than did those not so exposed. Following these experiments, two sisters who had been simultaneously poisoned by CO were observed, the one being treated in the usual manner and the other in precisely the same way with the addition of forty minutes' exposure, during treatment, to the mercury-vapor lamp. The irradiated patient showed a much more rapid elimination of CO and a much more rapid recovery of consciousness than did her sister. The irradiation employed was sufficiently intense to produce as its only unfavorable result a moderate degree of burning of the skin. Although this is the only controlled observation on man, the author finds in other cases evidence that the addition of radiation therapy is beneficial in the treatment of CO poisoning.

Clinical Observations on the Depressant Action of Insulin Upon the Genital Organs.—LEVAI (*Med. Klin.*, 1930, 26, 313) states in detail his observations on 3 patients, 1 man and 2 women, in whom the functions of the genital organs were markedly depressed by the more

or less continued administration of small doses of insulin given for the purpose of improving nutrition. All patients were nondiabetic. In the case of the man impotence was produced, while both women endured periods of amenorrhœa. In none of these patients was it possible, by the most searching examination, to discover any organic reason for the disturbances in their sexual functions, and in all 3 spontaneous recovery took place after cessation of insulin. Similar instances have not been found in the literature, but the author is able to support these human observations by references to similar depressant actions upon the sexual organs observed in experimental animals. He believes that insulin probably brings about these effects through a disturbance in the balance between several of the endocrin glands. In view of his findings he warns against the indiscriminate administration of insulin for the purpose of improving nutrition, and definitely opposes its employment when the improvement in nutrition is sought for purely cosmetic reasons.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Early Diagnosis of Whooping Cough.—McGEE (*Va. Med. Monthly*, 1930, 57, 165) made a positive diagnosis of this disease in 64 cases from the character of the cough, presence of an epidemic or history of exposure, the usual absence of any marked signs of bronchitis, laryngitis and postnasal discharge with a leukocytosis, showing as an absolute and relative increase in lymphocytes. The cough that was considered suspicious was an afebrile one, paroxysmal and spasmodic in character, which increased in intensity and was worse at night, and which failed to respond to usual treatment. White and differential blood counts were made after the child had had the suspicious cough lasting from seven to ten days. In 14 of these cases a negative diagnosis was made after a cough lasting from ten to twenty-one days. In no afebrile disease with cough is there so great a leukocytosis with such a high percentage of lymphocytes. The leukocyte counts in this series varied from 10,000 to 46,000 with an average of 19,273 leukocytes, while from 50 to 90 per cent of lymphocytes were noted with an average of 68.2 per cent.

Whooping Cough; Early Diagnosis by the Cough-plate Method.—SAUER and HAMBRECHT (*J. Am. Med. Assn.*, 1930, 95, 263) claim that the cough plate is the best means of early diagnosis. The disease can now be diagnosed before the lymphocytosis and whoop. It is early in the disease that a correct diagnosis is most important because it is then that the pertussis bacillus is present in its greatest numbers, whereas it is seldom found after the whoop has developed. In an analysis of 200 cases, they found that the plate was positive in all but 1 of 53 patients in the catarrhal stage; in 70 of 107 in the paroxysmal

stage and in none of 40 in the period of decline. These figures are in agreement with those published by others. A negative plate does not exclude whooping cough. The two most frequent errors in technique are that plates are not well enough coughed upon or that they are made too late in the disease. It is pointed out that this method of early diagnosis should not be compared with the throat culture in diphtheria. In the latter disease the lesion is accessible and the organisms are constantly present. In pertussis the lesion is not accessible and the causative organism as a rule can be isolated only early in the disease. The chief value of the early diagnosis is that the patient and the susceptible children with whom he has been in contact may be quarantined before they in turn expose others. In this way the incidence and the mortality may be lowered.

Viosterol; Prophylactic and Therapeutic Dosage.—HESS, DALE and KLEIN (*J. Am. Med. Assn.*, 1930, 95, 316) state that several factors must be given consideration in the determination of the prophylactic dose. It is obvious from the knowledge of the pathogenesis of rickets that insufficient mineral deposition during fetal life as seen in twins and premature infants, rapidly growing infants and babies with repeated infections and diarrhea, must be given special consideration. From blood chemistry determinations, 10 drops of viosterol in oil a day was the smallest dose that prevented a fall in both calcium and phosphorus from the first to the later months of the first year of life, although in 2 cases under their observation in which there were diarrhea and infection even 20 drops daily was inadequate to prevent a fall in calcium and phosphorus. They had no infant on more than 10 drops of viosterol a day to develop rickets as evidenced by clinical, roentgenographic or blood chemical studies. As regards the optimum therapeutic dose, it was impossible to arrive at a positive conclusion from the small group observed. The degree of rickets must be considered in every case. It was found that mild rickets would heal frequently on a dosage of from 10 to 15 drops of viosterol in oil daily while other cases would require larger doses. In some severe cases 15 and even 20 drops did not prove adequate. Infants on 30, 40, 50 and 60 drops showed uniform healing clinically, chemically and by roentgenogram. Toxic symptoms were not observed in any of the infants during the period of observation. The authors do not wish to state that toxic symptoms may not be produced by large enough doses of viosterol, but their investigation showed a large factor of safety in the administration of larger doses of viosterol, at least over limited periods of time.

The Use of a Modified Drinker Respirator in the Treatment of Asphyxia Neonatorum.—MURPHY and COYNE (*J. Am. Med. Assn.*, 1930, 95, 335) report the use of this apparatus in 5 cases of asphyxia neonatorum, with the result that 2 infants survived and 3 died. They feel that none of these babies would have survived had they not been treated with the mechanical respirator. They doubt if the respirator was responsible for the initiation of the respiration, though it may have had a stimulating effect on the respiratory center. The fairly constant increase in respiratory power exhibited by infants during two periods of observation, indicates that the respiratory supplied adequately the ventilation needs of these infants during the period before their respira-

tory centers began to function. It was not surprising that 3 of the infants succumbed in view of the conditions surrounding their births. As far as could be learned the use of the mechanical respirator played no part in causing these deaths. The 2 infants that survived would in all probability have died had it not been for their prolonged mechanical artificial respiration. At least the mechanical respirator supplied an adequate degree of ventilation over a long period of time. This is the most important point in asphyxia neonatorum. It is of the greatest importance to remove the mucus from the respiratory tract before beginning the operation of the apparatus. The advantages of this method are that it is perfectly safe as has been demonstrated by the authors. In addition it is possible to institute treatment in a few seconds and to maintain it over a prolonged period. Normal rate and depth of respiration can be closely simulated and adequate ventilation can be secured. A temperature can be maintained that throws no undue load on the metabolic activity. Free drainage of the respiratory passages can be maintained by adjusting the position of the child. The old and violent methods of resuscitation are avoided, and the complications incident to them are prevented.

Calcium Therapy During Childhood.—OCHSENIUS (*Münch. med. Wchnschr.*, 1930, 77, 804) emphasizes the great significance of calcium therapy in pediatrics, especially in the treatment of rickets. The administration of calcium in the form of calcium water is of no particular value because in rickets the organism is not able to absorb the calcium even though the food contains an ample supply. The retention capacity for calcium is increased by ultraviolet irradiation, by cod-liver oil that contains phosphorus, and by viosterol. The author recommends the following combination: 25 gm. of tricalcic phosphate, 0.2 gm. of phosphorus, 5 gm. of viosterol and 250 gm. of cod-liver oil. Of this mixture the child should receive one teaspoonful twice a day. If the rickets is complicated by a neuropathy, spasmodophilia results and tetany is either manifest or latent. In these conditions large doses of calcium are of great help, because the calcium quickly counteracts the nervous irritability. The sedative effect of calcium has been demonstrated in experiments. It has also proved helpful in the exudative diathesis, especially in the weeping eczema that is accompanied by pruritus. The itching is dependent on the condition of the nervous system and the administration of large doses of calcium counteracts it. It also has a drying effect on the eczema. Children with asthma and those with relapsing bronchitis may likewise be treated with calcium. A difficulty in calcium administration is its unpleasant taste, which may be disguised by the addition of cocoa.

Scarlet Fever; Second Attacks.—GABRIEL and ZISCHINSKY (*Jahrb. f. Kinderh.*, 1930, 127, 253) use the term "recurrence" only for the rare cases in which both the development and the clinical picture indicate an exacerbation of an old latent scarlet fever, and in which there is little probability of a new exogenous infection. To all cases in which these conditions are not fulfilled, they apply the term "second attack." In more than 20,000 cases of scarlet fever that were seen by them in a period of seventeen years they found 387 cases of "second attack,"

or a percentage of 1.9. The curves of the frequency of first attacks and second attacks ran approximately parallel. As predisposing factors for the development of second attacks of scarlet fever, there are noted wounds of various sorts, measles, chicken-pox and serum disease. The most common predisposing factor was a recurrence of the first attack. The course of second attacks of scarlet fever is usually more severe than in first attacks and complications are more frequent.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Bismuth in the Treatment of Syphilis.—LEVADITI (*Am. J. Syphilol.*, 1930, 14, 156). For the past nine years, Levaditi, Fournier and their associates have used bismuth in the treatment of syphilis practically to the exclusion of all other drugs. Levaditi reaffirms his principles previously reported by him, which include: (1) Bismuth has a curative and preventive action in early and late syphilis; (2) it causes the rapid disappearance of the spirochete from the early lesion; (3) it sterilizes the lymphatic glands; (4) it causes a favorable modification of the reactions of the blood and spinal fluid; (5) bismuth exercises a profound and lasting curative action in syphilis—principally because of its delayed elimination; (6) bismuth acts where arsenic fails (in arsenic-resistant cases). To these earlier principles Levaditi has added: (7) Bismuth is superior to arsenical therapy with the exception of the prompter sterilizing qualities of the intravenous arsphenamins; (8) bismuth is absolutely innocuous, providing neither intravenous bismuth nor the water-soluble intramuscular preparation is used; (9) bismuth is superior in its therapeutic properties to mercury, and (10) bismuth therapy is efficacious not only in acquired syphilis but also in hereditary and congenital syphilis. The author devotes considerable space to a discussion of the proper preparation and salt of bismuth to be used. He believes that the most efficacious type is either the insoluble bismuth salts in oil suspension or the fat-soluble compound. The main criteria in choice depend on the formation of bismuth deposits in the body with the subsequent formation of bismoxyl, and the actual amount of metallic bismuth contained in the preparation. He names three classes of bismuth compounds as meriting consideration: (1) The iodo-quinin salts of bismuth; (2) the oxids or oxycarbonates of bismuth, and (3) the fat-soluble derivatives. He favors the use of the latter type of bismuth compound and particularly a-carboxethyl; b-methyl-nonoate of

bismuth (biliposol). Its bismuth content is 0.04 gm. per 1 cc. of the oily solution. Experimentally the curative dose varies from 1 to 2 mg. of metallic bismuth to the kilogram of body weight. The sterilization of local lesions is prompt and its effect on the Meinicke reaction is comparable to the arsphenamins. Clinically the salt is employed in bi-weekly intramuscular doses of 2 cc. of the oil in a series of from ten to fifteen injections. The salt is well tolerated and evidence has been gathered that the radiographic bismuth shadows are more diffuse and less opaque than those of insoluble oily suspensions of bismuth. Renal elimination commences rapidly after the injection and is demonstrable up to one and a half to two months after the cessation.

(The report together with the continental bibliography appended bears evidence that the original enthusiasm of Levaditi and his associates in the exclusive use of bismuth has not declined.)—EDITOR.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Hysterosalpingography.—In a well-presented and excellently illustrated article, WITWER, CUSHMAN and LEUCUTIA (*Am. J. Roentgenol.*, 1930, 23, 125) present their views on the present status of hysterosalpingography as a diagnostic measure. They assert that the use of iodized oil for outlining the female genital organs is a simple and safe procedure, since in a series of 512 cases the only accident observed was that of a ruptured tube, which did not lead to any ill effects. The method is of great diagnostic value in developmental anomalies of the genital organs, in tubal conditions leading to sterility, in certain carefully selected cases of pregnancy in which therapeutic abortion is indicated or a differential diagnosis from other obscure conditions is essential, in uterine tumors excepting malignant ones and in certain extrauterine neoplasms. The contraindications to the use of the method are recent hemorrhage, inflammatory conditions that are not completely quiescent, active infections or malignant growths involving the cervix, previous intrauterine interventions, ectopic gestation or intrauterine gestation in which a therapeutic abortion is not desired, infected cervical or uterine polyps and fever. In certain instances the injection of iodized oil is of direct therapeutic value. The most important practical value of hysterosalpingography in connection with extrauterine tumors is in the differentiation between these and large uterine

fibromas, when an accurate diagnosis cannot be made by the usual methods of gynecologic examination. It is advisable in such instances to outline the margin of the tumor by a lead wire placed on the abdominal wall during the taking of the roentgenogram and then to analyze the relation of the uterine cavity to the lead wire. If the uterine cavity appears of normal shape and size, but on the periphery of the lead wire, the condition is that of a cyst, while if the uterine cavity is enlarged, distorted and appears in the center or near the center of the lead wire, the condition is that of a uterine fibroma. The addition of roentgenograms in the lateral view will occasionally aid in further substantiating the diagnosis. They describe their technique in detail which is generally similar to that used by most other workers in this field and is extremely simple.

Results of Treatment in Cancer of the Cervix.—In a most comprehensive statistical study, embracing the material of many of the larger European clinics, FELDWEIG (*Zentralbl. f. Gynäk.*, 1930, 54, 779) has presented the results which have been attained by the various methods of treatment in most of the usual types of carcinoma of the female genital organs. In looking over his tables concerning carcinoma of the cervix, it is seen that whereas operation has given an absolute cure rate of less than 20 per cent in over 5000 cases, irradiation is somewhat better, but the combination of operation and irradiation is probably the best of all, giving absolute cure rates varying from 18 to 27 per cent. These figures may seem low to some of our readers, but it must be remembered that they refer to absolute cure, that is, the number of patients cured out of the total number seen, irrespective of the fact that many of the cases were beyond help and were given no treatment. When we come to the relative cures, that is, the number of cures obtained from the number of patients actually treated, naturally the figures are much more promising. In this classification we find that operation alone gives 35 per cent and operation plus irradiation or irradiation alone give about the same results, except in Heyman's statistics, where irradiation gives over 46 per cent relative cures. These statistics of relative cures apply only to the so-called operable cases, and it is well known that operability varies with the individual clinic, as is shown in this study where it varies from 14 to 62 per cent. In spite of the popularity of the Wertheim operation in Germany, the author is of the opinion, as the result of this study, that it should no longer be considered as a standard method of treatment by itself. It is no longer a question of operation or irradiation in a given case, but rather should the patient receive operation and irradiation or only irradiation.

Biologic Test in Diagnosis of Chorionepithelioma.—The value of the test which has been described by Aschheim and Zondek in the diagnosis of pregnancy seems to be fairly well established. For the benefit of those who may not be familiar with it, the test is based upon the proven fact that pregnant women excrete large amounts of hypophyseal hormone in the urine. When the urine from pregnant women is injected into infantile mice, corpora lutea and hemorrhages are formed in their ovaries. As a result of many tests, it is claimed to be positive in 98 per cent of the cases of pregnancy, even in the early days. In cases of

ectopic gestation and abortion the test is positive as long as living fetal tissue is in biologic contact with the blood of the mother. In an article by ASCHHEIM (*Am. J. Obst. and Gynec.*, 1930, 19, 335), who is one of the discoverers of the test, in addition to emphasizing the value of the test in the types of cases mentioned, he states that the test has been found strongly positive in hydatidiform mole and in chorionepithelioma. In one instance it was twelve times stronger than the reaction usually obtained in the second month of gestation (measured by the minimum dose of urine, which gave a positive mouse test). Since there is no embryo in hydatidiform mole, it must be the living tissue of the mole that is responsible for the reaction. He feels that one should make this test whenever there is a clinical suspicion of chorionepithelioma and always after a hydatidiform mole has been expelled. The test, however, may remain positive after hydatidiform mole as long as two months without evidence of chorionepithelioma, so that this must be taken into consideration.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

Meatless Diet as a Therapeutic Measure in Ménière's Disease.—Ménière's disease is characterized, in the order of their appearance, by tinnitus aurium, severe vertigo, nausea, vomiting and in many cases deafness. These symptoms usually reach their height within an hour and then slowly disappear in reverse order. Because Ménière's historical case (1861) was associated with intralabyrinthine hemorrhage, this lesion for a long time was regarded as the sole cause of the condition. It is now recognized that the symptoms may be due to a variety of infectious and metabolic states and vascular derangements affecting the vestibular (and often the cochlear) mechanism directly or indirectly. For this reason, and because vertigo is its outstanding symptom, many instances of vertigo have been regarded erroneously as Ménière's disease. Therefore, it is important that a proper diagnosis be made, so that a clearer conception of the etiology, pathology, prognosis and treatment be obtained. Consequently, any contribution tending to clarify our none too concise ideas of Ménière's disease should be welcomed. In this connection, MUCK (*Klin. Wchnschr.*, 1930, 9, 491) offers a diagnostic and a therapeutic suggestion. Interpreting the vasostrictor nasal reflex—as manifested by the "mucographia alba" and produced by applying epinephrin to the mucosa of the turbinal—as an indication of altered intracranial vascular innervation, the author regards its presence in Ménière's disease as proof of a causal angiospasm of the auditory artery. Because the same reflex has been produced in epilepsy and in migraine, and because both of these conditions have responded in certain instances to a meatless diet, the author withdrew meat from the diets of several patients suffering from recurrent attacks of Ménière's disease. Those who strictly adhered to the right dietary régime were improved.

Analogies in Picture in Otosclerosis and Juvenile Diseases of Epiphysis.—Investigators into the cause and nature of otosclerosis have remarked about its occasional association with certain conditions of abnormal osseous development, such as osteogenesis imperfecta, and have observed a histopathologic similarity between otosclerosis and some types of diseases of bone, notably the localized forms, osteodystrophia fibrosa (ostitis fibrosa). In this connection we take the liberty to quote from the *Journal of the American Medical Association* (1930, 94, 2033) that LEIRI (*Finska läk.-sällsk. handl.*, 1930, 72, 206) "asserts that many and important features are seen in both disorders" (otosclerosis and juvenile diseases of epiphysis). "He expressly states that mechanical irritation, while it plays a significant part in the development of otosclerosis, is no more the primary cause in otosclerosis than in juvenile diseases of the epiphysis."

Mixed Tumors of Palate.—Mixed tumors of the palate present the same distinctive histologic complexities and clinical benignancy as those occurring in other oral-fascial structures, especially the parotid gland, of which they constitute the characteristic neoplasm. Palatal mixed tumors are rare. Probably less than 100 cases are on record. Of these approximately one-half have been encountered in the soft palate. D'AUNOY (*Am. J. Path.*, 1930, 6, 137) reports 2 cases of palatal mixed tumor in females, aged twenty-five and forty-three years respectively. In the younger individual the new growth occupied the soft palate. SONNENSCHNIG (Mixed Tumors in the Soft Palate: Reports of Two Cases and a Survey of the Recent Literature, *Arch. Otolaryngol.*, 1930, 11, 137) also describes 2 mixed tumors which were removed from the soft palates of 2 men, each twenty-nine years of age. Both authors recognize the theory of embryonal enclavement as a satisfactory explanation of the origin of these tumors. Furthermore, they agree that they are essentially benign, even though the microscopic picture is often suggestive of malignancy. Each writer, too, calls attention to the likelihood of local recurrence, particularly after incomplete surgical removal. Treatment consists in operative ablation, except when the growth involves vital structures. When surgical intervention is contraindicated roentgen therapy is said to be efficacious.

A Consideration of Peritonsillar Abscess With a Rational Surgical Method of Relief.—In peritonsillar abscess one meets a condition sufficiently common in occurrence, painful and debilitating in its course, serious in its complications and sequelæ and refractory of customary therapeutic measures to command the utmost respect and attention. As a rule, it is apparent that the prevailing operative approach *via* the palate leaves much to be desired in the surgical management of many of these cases. By taking advantage of a more natural point of access to those peritonsillar abscesses situated in the supratonsillar fossa, DOBBS (*Laryngoscope*, 1930, 40, 186) describes a method whereby the successive insertions of graduated screw instruments in the cleft beneath the plica semilunaris affects adequate evacuation and drainage of the pus with a minimum amount of pain, hemorrhage and danger to the patient. A companion article by PELZ (*Ibid.*, p. 190) elaborates the instrument and site of approach.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

The Status of Ultraviolet Ray Therapy in Diseases of the Skin.—From a review of the literature and his own experience, SCHILLER (*Radiology*, 1930, 14, 576) arrives at the opinion that very few skin diseases can actually be treated with greater benefit by the ultraviolet rays than by other measures. Those which can are the tuberculous lesions of the skin and the group of septic conditions including septic wounds and ulcers. In other groups the ultraviolet ray has proved to be either a more or less indifferent agent or, at best, an adjunct to general treatment. While the use of ultraviolet in proper hands is accompanied by a minimum amount of risk it is not as foolproof as some believe, and cannot be put into the hands of the public for indiscriminate application. For example, superficial ulcerations which heal slowly and leave a suspicion of malignancy can be produced by overdosage, and many cutaneous diseases are aggravated by light.

The Value of a Lateral View in the Diagnosis of Pregnancy.—For the roentgenologic diagnosis of early pregnancy and multiple pregnancy GRIER (*Radiology*, 1930, 14, 571) considers the lateral view to be decidedly more reliable than anteroposterior. When a pregnant woman lies on her side the uterus occupies the anterior part of the abdomen and the total dimension of the tissue to be penetrated by the rays is considerably less than when she lies on her back, and a clearer image of the fetus is obtained. In the later months of pregnancy, after the fetal head has descended into the pelvis the anteroposterior view is preferable.

Phytobezoar in the Stomach.—In 1928 Maes collected 139 cases of bezoars, of which 23 were phytobezoars. Of the latter, persimmon-seed balls seem to be most common, probably because of the high percentage of gum and pectin in such masses. CAMP (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 413) reports an additional case. The patient had been well until two and a half months previously, at which time he had eaten a large quantity of persimmons. Gradually he began to have epigastric distress with a sensation of pressure and grinding about three hours after meals. In view of the history a persimmon-seed ball was suspected clinically. The roentgenologic examination with the barium meal revealed an extensive mottled central defect in the gastric shadow, characteristic of a bezoar. At operation the mass of persimmon seeds was found to be 15 cm. in length and 5 cm. in diameter. There was also a subacute gastric ulcer, with a shallow crater, on the posterior wall just below the angle.

Echinococcic Involvement of Bone.—Echinococcus cysts in man occur rarely in the United States and Canada, and the bones are involved in less than 2 per cent of the cases. STONE (*Radiology*, 1930, 14, 557) reports an instance in which the cysts were situated in the ilium and sacrum. Starting as a small cyst, echinococcus involvement of bone develops into a multilocular cyst with many small ones in the immediate vicinity. There is no sequestration, no atrophy and no increased calcification. Any bone may be affected, but the pelvis, femur, humerus and tibia are the commonest sites.

In the same issue of *Radiology* (p. 562) Hsieh reports a case observed at Peiping, China, in which the pelvic bones and the head and neck of the right femur were involved.

Observations on the Clinical Value of the Roentgen Ray in the Diagnosis of Cardiovascular Disease.—The Roentgen ray affords by far the most accurate measurements of heart size and shape that can be obtained, in the opinion of WHITE (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 353). In the presence of obesity, emphysema and other complications which render physical examination of the heart very imperfect, the Roentgen ray sometimes affords the only means of determining heart size and shape. Surprising and unexpected findings, such as pericardial calcification or aneurysm of the aorta are sometimes revealed only by Roentgen study. The size of the aorta and of the left auricle, occasionally also of the left ventricle, can be determined only by the Roentgen ray. Abnormalities of the hilus shadows and of the pulmonary artery are important findings which can be discovered only with the Roentgen ray. Observation of peculiarities in pulsation of the heart and great vessels is alone worth the trouble of applying this method of study.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

Unusual Case of Cerebrospinal "Giant Cocci" Meningitis.—WEINBERG (*J. Nerv. and Ment. Dis.*, 71, 412) observed a case in which no typical meningococci were found, but after repeated examinations "giant cocci" were found. The patient recovered rapidly following the administration of 10 cc. of antimeningococcic serum intracisternally, whereas treatment by the lumbar and intravenous routes had been unsuccessful. The author believes that large doses of serum are not necessary in the treatment of meningitis, and that repeated lumbar puncture may do considerable damage. The bacteriologic discussion is presented by Robert Koch.

Syndromes of Tumors in the Chiasmal Region.—DEERY (*J. Nerv. and Ment. Dis.*, 1930, 71, 383) presents 170 cases receiving a transfrontal operation which presented clinical evidence of "chiasmal syndrome." The cases are recorded as follows: Pituitary adenomas, 54; craniopharyngeal pouch cysts, 47; suprasellar meningiomas, 16; cases with negative findings, 15; gliomas of the optic chiasm, 14; question of chronic arachnoiditis, 13; third ventricle tumors, 4; aneurysm, 3; cholesteatomas, 2; sphenoidal ridge meningioma, 1; angiomatous malformation, 1. The preoperative and postoperative diagnoses are compared with a view to clarifying the differential diagnoses between the various subgroups. Pituitary adenomas had been misdiagnosed as craniopharyngeal pouch cysts in 9 cases; suprasellar meningiomas in 7; olfactory groove meningioma in 1; third ventricle tumor in 1. Of the 9 cases considered to be craniopharyngeal pouch cysts, 3 showed suprasellar calcification and 1 showed intrasellar calcification, indicating that calcification does occur at times in pituitary adenomas. Cases misdiagnosed as suprasellar meningiomas all showed suggestive evidence of dyspituitarism. "If a middle-aged person presenting this differential problem shows a perfectly normal sella and no signs of pituitary dysfunction, one can reasonably expect to find a small meningioma. If either sellar changes or signs of pituitary dysfunction are present the diagnosis is a little less safe to make. On the other hand, as already stated, all adenomas need not markedly change the sella." Anosmia and uncinatc attacks led to the diagnosis of one pituitary adenoma as olfactory groove meningioma, although characteristic mental findings were absent. As to this group, the author believes that clinical evidence of the dyspituitarism when found is unsafe to disregard; a normal appearing sella or calcification within or above it are both found in patients with pituitary adenoma; a large adenoma with widely distended sella may occur at a very early age; either homonymous field defects or choked disks may occasionally be caused by adenomas. The craniopharyngeal pouch cysts showed a rather typical history of gradual dimness of vision and frontal headaches over a period averaging two years. Visual defects were present in all cases with asymmetrical defects as a rule. Complete blindness occurred in 1 and good vision in both eyes in 1. Practically all of these cases showed evidence of pituitary insufficiency, and suprasellar calcification occurred in 72 per cent. Twelve cases were incorrectly diagnosed before operation. The other lesions causing the chiasmal syndrome are analyzed in a somewhat similar way. The author calls attention to the fact that there is a strong clinical similarity between the groups, and there is considerable possible variation in the syndrome itself.

The Rôle of Psychological Factors in the Production of Organic Nervous Disease.—RABINER and KESCHNER (*J. Neurol. and Psychopathol.*, 1930, 10, 311) state that many patients who are diagnosed as functional later show undoubted evidences of organic nervous disease. This raises the question as to what relationship may exist between the functional and organic syndromes presented. The clinical experience of these authors suggest to them that some organic nervous diseases may occur in two phases, the early, psychic, and the later, organic; that the transition between these two phases is imperceptible and can only be

appreciated when patients remain under prolonged observation by the same observers. They briefly review the literature on the influence of function on structure, and present a thesis that abnormal lipid metabolism due to psychic factors may produce structural changes in the central nervous system which may account for the organic clinical picture manifested later. They present briefly three cases which were diagnosed as functional in the beginning and later developed dystonia musculorum deformans. (The thesis presented is general in its implications, but the evidence cited applies only to this particular organic disease.)

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Radiogenic Microcephaly: A Survey of Nineteen Recorded Cases, With Special Reference to Ophthalmic Defects.—GOLDSTEIN (*Arch. Neurol. and Psychiat.*, 1930, 24, 102) observed severe disturbances of the central nervous system of children irradiated *in utero*. Of 75 children so exposed, 20 (26.6 per cent) exhibited marked defects, 18 (24 per cent) being microcephalic idiots. In previous papers the conclusion is reached that pelvic radiotherapy during pregnancy is extremely injurious to the fetus. The ocular defects of 19 children whose defects were believed to be due to irradiation *in utero* were thought to be due to inhibitions of development of the central nervous system, as manifested by microcephaly at or shortly after birth. Sixteen women were treated with the Roentgen ray, 2 with radium and 1 with mesothorium, relatively large doses being given to all the women. Many of them received more than one Roentgen treatment. Fifteen women received radium therapy during the first four months of gestation, and several of them were given one or more treatments in the first month. The indications for radium therapy were pelvic disease, tuberculosis, peritonitis, functional metrorrhagia, amenorrhea and sarcoma of the ovary. In 2 women abortion was attempted by the use of the Roentgen rays. Reports were available concerning ocular defects in 15 of the 19 children born to these 16 mothers. The various eye disturbances were given as ankyloblepharon, 3; bilateral chorioretinitis, 2; optic atrophy, 3; strabismus, 5; nystagmus, 2; microcornea, cataract, defect in the retina, abnormal retinal pigmentation, albinic fundus and epicanthus, each once. Some children exhibited more than one defect. Microphthalmia was present in 7 children. Other optic defects were associated with the microphthalmia. Four children were almost completely amaurotic, the blindness being due to optic atrophy, chorioretinitis or to both.

It is known that of 15 children exposed to irradiation in the first four months of gestation, 11 (73.3 per cent) manifested disturbances of the eye. The remaining 4 children were irradiated for the first time during or after the fifth months of gestation. It was observed that of the 14 microcephalic children who had the round, small type of head, 8 (57 per cent) manifested disturbances of the eye while 3 (21 per cent) did not. The probable connection between fetal irradiation, malformation of the skull and the occurrence of ophthalmic defects is a matter for later discussion.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

An Epidemic of Influenza in an Isolated Community—Northwest River, Labrador.—SMILLIE (*Am. J. Hyg.*, 1930, 11, 392) studied an epidemic of influenza which occurred in Northwest River, an isolated community in Labrador, in 1928. The date of introduction of the disease into the community was known and it was possible to trace the epidemic throughout its course. It seems probable that the virulence of the infective agent remained fixed, and the dosage was uniform. There occurred, however, a marked variation in resistance of various individuals to infection. It seems probable that this resistance was nonspecific. The infective agent disappeared completely from the community in a short time, for a presumably highly susceptible group of Indians entered the community one month after the last case had occurred and none of them were affected.

Effect of Repeated Daily Exposure of Several Hours to Small Amounts of Automobile Exhaust Gas.—The Public Health Service (*Pub. Health Rep.*, 1929, 44, 1260) gives the following data on the effect of carbon monoxid in gasoline engine exhaust gas: *With the subjects at rest or exercising mildly:* (1) Exposure to 2 parts of CO in 10,000 caused: (a) in 2 hours, slight but not discomforting symptoms in some subjects; (b) in three and a half to four hours, distinct frontal headaches of a discomforting nature in some subjects; (c) in six and a half hours no occipital headaches occurred in any subjects and no symptoms of any kind were experienced in 50 per cent of the exposures; (d) in three and a half to four and a half hours a blood saturation of 20 per cent; (e) in five to six hours a blood saturation of 25 per cent. Saturation above 25 per cent was attained very slowly. (2) Exposure to 3 parts of CO in 10,000 caused: (a) in less than two hours slight symptoms in some

subjects; (b) in two and a half to three hours distinct frontal headaches in some subjects; (c) after three hours a few occipital headaches and cases of vertigo; (d) in five hours distinct discomforting symptoms in more than 65 per cent of the subjects; (e) in two and a half to three and a half hours a blood saturation of 20 per cent; (f) in three to four hours a blood saturation of 25 per cent; (g) in four to four and three-quarter hours a blood saturation of 30 per cent. (3) Exposure to 4 parts of CO in 10,000 caused: (a) in one and a half to two hours frontal headaches, in some subjects; (b) in two and a half to three and a half a few occipital headaches; (c) in three and a half to four hours more than 90 per cent had distinct frontal headaches. (d) in one and a half to two and a half hours a blood saturation of 20 per cent; (e) in two and a half to three and a half hours a blood saturation of 25 per cent; (f) in three to four hours a blood saturation of 30 per cent. (4) The results of the control tests showed that a few cases of headache occurred, but the number was probably no greater than might be expected in any group of normal men. There was no distinct difference in the character and number of symptoms when exhaust gas was entirely absent from the air as compared with experiments when the air contained exhaust in which the CO was reduced to an insignificant amount by carbureter adjustment. Although there was a tendency for headaches to appear with a lower amount of CO hemoglobin when the latter was attained by exposure to the lower concentrations of carbon monoxid, in general, frontal headaches began in some subjects only when the saturation reached 18 to 20 per cent. A few occipital headaches accompanied by vertigo distinctly occurred at 23 to 28 per cent. *With exercise:* even though of a mild form, exercise distinctly augmented the absorption of CO and caused symptoms to appear after shorter exposure. Exercise immediately after exposure markedly increased the speed of elimination, but this procedure is not recommended or advised as a treatment for poisoning by CO. Until the supply is exhausted, single copies of this bulletin may be had free upon application to the Surgeon General, United States Public Health Service, Washington, D. C. Additional copies may be purchased from the superintendent of Documents, Government Printing Office, Washington, D. C., at 15 cents per copy.

Fatty Degeneration of the Liver and Kidneys in the Dog Apparently Associated with Diet.—SEBRELL (*U. S. Pub. Health Rep.*, 1929, 44, 2697) was feeding dogs a diet designed to produce blacktongue, a condition in the dog which is highly analogous to pellagra in man. Certain of the dogs presented a very extensive and readily recognized fatty degeneration, especially of the liver and kidneys, though they may or may not have presented evidence of blacktongue. The condition could not be recognized by a competent veterinary pathologist, and attempts to transmit it by inoculation failed. The condition seems to be of dietary origin.

The Fate of Tubercle Bacilli in the Organs of Reinfected Rabbits.—LURIE (*J. Exper. Med.*, 1929, 50, 747) states that in the presence of a certain amount of residual primary lesions, human or bovine tubercle bacilli of reinfection are destroyed in all the organs of rabbits without any preliminary multiplication. This destruction is not quite complete;

a few organisms persist even two months after reinfection. No macroscopic tuberculous lesions due to the reinfection develop in these rabbits. With the practical disappearance of the primary lesions and their enclosed organisms, restricted multiplication of the bovine bacillus of reinfection takes place but not the extensive growth of the virus observed in rabbits after a primary infection. In these rabbits slight tuberculous lesions develop as compared with the massive tuberculosis of primarily infected rabbits. The human tubercle bacillus of reinfection does not multiply at all, nor does it cause any lesions, even when the lesions of the primary infection have almost disappeared. Although the rabbit destroys efficiently considerable quantities of bovine tubercle bacilli of reinfection introduced from without, it may harbor innumerable human bacilli in the residual primary lesions of the lung and kidney.

Pasteurized Dried Fruits.—FELLERS (*Am. J. Pub. Health*, 1930, 20, 180) claims that dried fruits harbor considerable numbers of molds and bacteria and also a few yeasts. It is desirable to protect the public against bacterial infection from these foods. At least one such outbreak has been reported. Dried fruits, such as dates, raisins, figs, apricots and prunes, may be pasteurized in paper cartons with moist heat at controlled temperatures and humidities. In general, different treatments are required for each fruit and often each variety must be handled a little differently. Temperatures which have been found effective in greatly reducing the total numbers of microorganisms on dried fruits at humidities of 70 to 100 per cent vary from 150° to 185° F. for thirty to seventy minutes. *Escherichia coli* and *Eberthella typhosum* were destroyed in every case where the temperature of the fruit remained at 160° F. or above for thirty minutes at relative humidities of 75 per cent or more. Commercial processes for the effective pasteurization of dates, figs and raisins are now being developed or used. Sulphured fruits harbor very few organisms because of the inimical effect of sulphur dioxide. Acid fruits are more easily pasteurized than those of higher pH. From a public health viewpoint, pasteurization marks a definite advance in the merchandising of dried fruits.

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ORIGINAL ARTICLES.

TREATMENT OF PERNICIOUS ANEMIA WITH DESICCATED,
DEFATTED STOMACH.

By CYRUS C. STURGIS, M.D.,

DIRECTOR, THOMAS HENRY SIMPSON MEMORIAL INSTITUTE FOR MEDICAL RESEARCH;
PROFESSOR OF MEDICINE; DIRECTOR, DEPARTMENT INTERNAL MEDICINE,
UNIVERSITY HOSPITAL, UNIVERSITY OF MICHIGAN,

AND

RAPHAEL ISAACS, M.D.,

ASSISTANT DIRECTOR, THOMAS HENRY SIMPSON MEMORIAL INSTITUTE FOR MEDICAL
RESEARCH; ASSOCIATE PROFESSOR, DEPARTMENT OF INTERNAL MEDICINE,
UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.

(From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.)

SINCE the report in 1926 by Minot and Murphy¹ on the efficiency of liver in inducing a remission in pernicious anemia, numerous substances have been tried with more or less success. These authors found that kidney was effective and this observation was confirmed by McCann.³ Castle² reported successful results with beefsteak treated with the gastric secretions of normal human beings, but was unable to develop the hemopoietically active substance by incubation of beefsteak with gastric mucosa in acid solution. Sturgis and Isaacs⁴ found that desiccated whole hog stomach and stomach defatted with petroleum benzine was very active in inducing remissions. These observations were confirmed by Conner,⁵ by Wilkinson⁶ and others. The present report deals with further studies of the effect of feeding whole, chopped, hog stomach (twelve to eighteen hours old) desiccated and defatted with petroleum benzine, to patients with true pernicious anemia.

STURGIS, ISAACS: PERNICIOUS ANEMIA

The stomach was prepared by removing the fat and surrounding mesentery, and chopping the material very fine. This was then dried at a low temperature and the fat removed by repeated washing with petroleum benzin. One hundred grams of fresh stomach yielded from 11.7 to 15 gm. of the dried material. The removal of the fat eliminated much of the odor, and the product had very little taste. It was fed to the patients as a thick purée in tomato juice, being eaten as one would a thick cereal. The dose was from 15 to 40 gm.

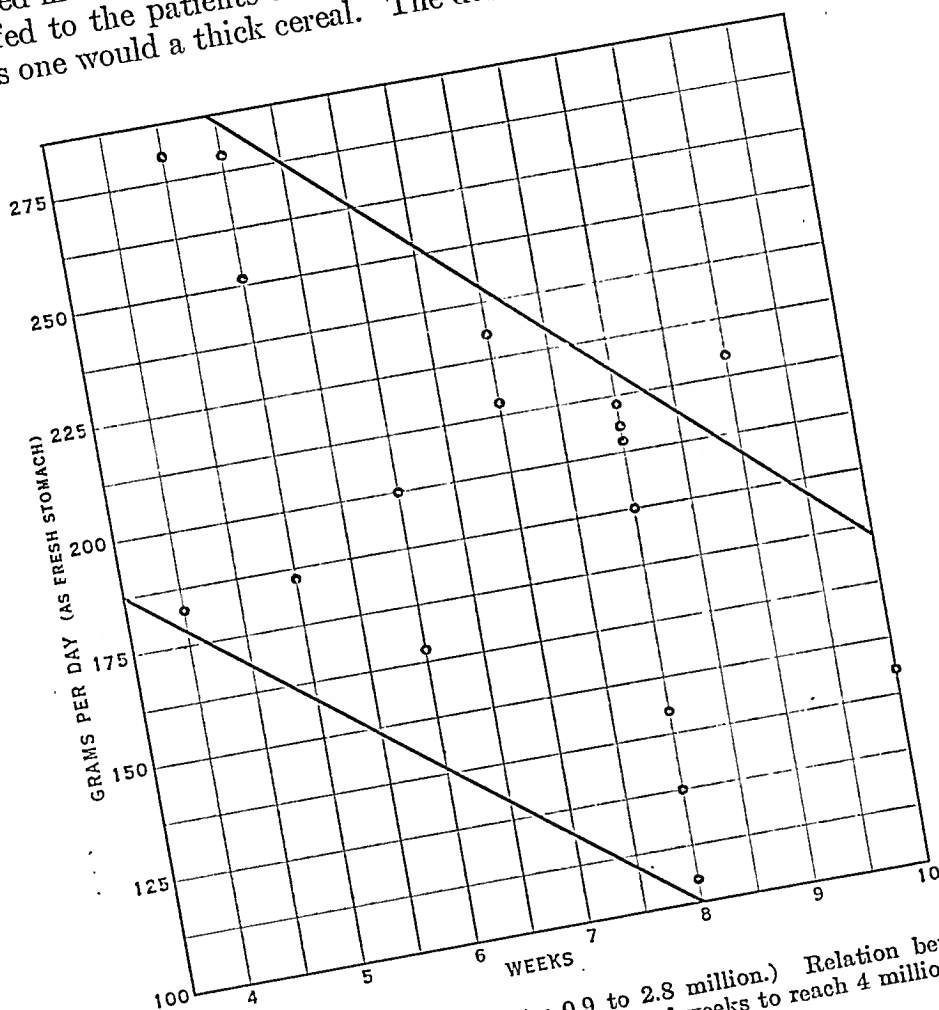


CHART I.—(Initial red blood cell counts; 0.9 to 2.8 million.) Relation between total amount of stomach per day and number of weeks to reach 4 million.

daily, representing 107 to 300 gm. of fresh stomach. The average dose of 20 to 28 gm. daily (145 to 150 gm. of fresh stomach) was found to be satisfactory in inducing a remission, and 7 to 10 gm. (50 to 70 gm. of fresh stomach) was found to be satisfactory as a maintenance dose. A safe dosage which has proven effective is 10 gm. for each 1,000,000 deficit in the red blood cell count. The subjective improvement was similar to that following the use of liver or liver extract, and up to the present no gross differences have been

noted in their actions on the neurological complications of the disease. There appears to be a definite correlation, within certain limits, between the dosage of dried, defatted stomach and the number of weeks required for the red blood cell count to reach 4,000,000 or more per cubic centimeter. This varies to some extent with the individual patient, the initial red blood cell count and the state of the bone-marrow at the beginning of the therapy. (Chart I.)

Table I shows that maximum reticulocyte percentages after stomach feeding, reached usually on the seventh or eighth day, compared with the calculated percentages, derived by Riddle⁷ from the formula of Minot, Cohn and their associates.¹

$$R = 0.73 - 0.2 E_o$$

$$R = 0.73 + 0.8 E_o$$

R = maximum percentage of reticulocytes observed during treatment

E_o = red blood cell count when treatment is begun.

TABLE I.

Patient No.	Before treatment.		Period of treatment, weeks.	After treatment.		Grams of stomach per day calculated as fresh tissue.	Maximum reticulocyte percentage.	Calculated maximum reticulocyte percentage.
	Red blood cells, millions per c.mm.	Hemoglobin per cent (Sahli).		Red blood cells, millions per c.mm.	Hemoglobin per cent (Sahli).			
1	0.9	30	5.0	4.1	75	187	14.1*	34.6-45.6
2	1.0	24	8.0	4.5	81	205	13.5*	31.7-38.0
3	1.1	29	6.0	4.0	77	200	18.8†	29.0-34.6
4	1.1	28	9.0	4.3	102	211	34.1	29.0-34.6
5	1.2	29	8.0	4.0	81	143	21.3†	26.5-31.7
6	1.2	33	4.5	5.6	79	281	36.4	26.5-31.7
7	1.3	25	4.0	4.5	76	187	36.0	24.3-29.0
8	1.3	30	7.5	4.2	72	107	24.1	24.3-29.0
9	1.6	40	8.0	4.5	76	125	17.8†	18.7-22.3
10	1.7	50	5.0	4.0	75	250	x	
11	1.8	44	8.0	4.0	80	211	13.6	15.6-18.7
12	1.8	38	7.0	4.3	85	230	x	
13	1.8	36	10.0	4.2	64	143	16.6	15.6-18.7
14	2.2	49	5.0	4.5	83	277	17.6	10.5-12.9
15	2.2	39	4.5	4.0	59	285	17.4	10.5-12.9
16	2.3	58	6.5	4.6	99	200	10.2	9.4-11.6
17	2.4	75	4.0	4.3	80	200	x	
18	2.4	62	6.0	4.5	90	206	4.8	8.4-10.5
19	2.8	64	6.0	4.1	82	165	5.1	4.9-6.6
20	2.8	51	7.0	4.5	83	215	5.9	4.9-6.6
21	2.8	71	8.0	4.2	94	206	5.7	4.9-6.6
22	2.8	57	8.0	4.0	84	187	3.3	4.1-5.7

* Had a "reticulocyte response" to liver therapy just before the treatment was started.

† Stomach not defatted.

x Data incomplete.

As Minot and his associates have so well shown, the reticulocyte response is an early evidence of the potency of a therapeutically active preparation for this disease. The table shows the initial red blood cell counts and hemoglobin percentages and the number of weeks before the count reached 4,000,000 per c.mm. or more, except for those patients receiving other treatment subsequently or under observation for too short a period. Chart II shows the actual maximum reticulocyte response in 21 patients during the first two weeks of treatment with dried, defatted stomach made from 107 to 285 gm. of fresh whole stomach, as compared with the

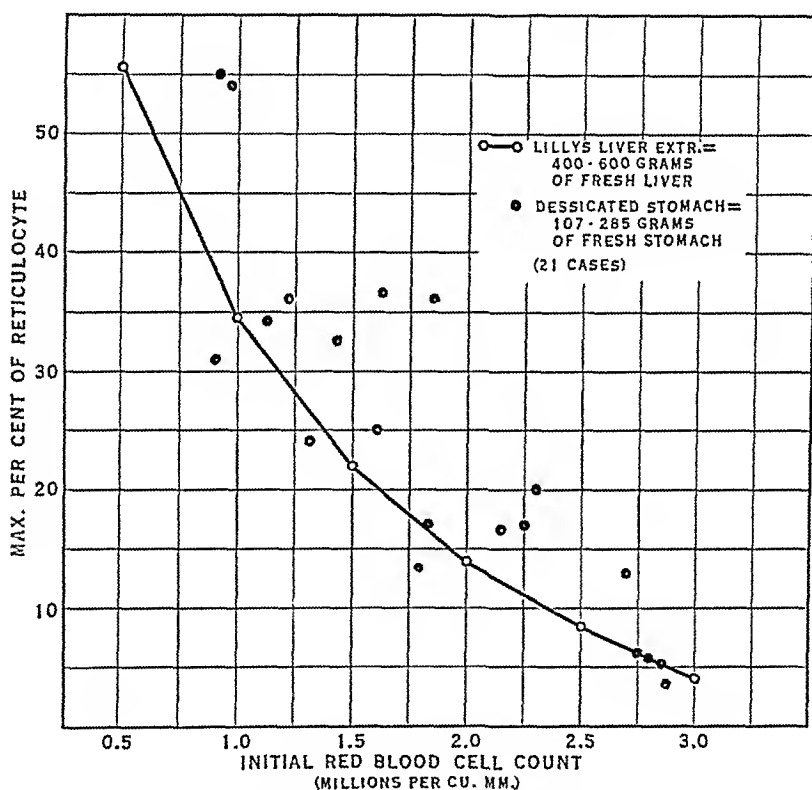


CHART II.—Relation of maximum reticulocyte percentage and initial red blood cell count.

reticulocyte response from a potent liver extract made from 400 to 600 gm. of fresh liver, in similar patients with pernicious anemia. Of 22 patients carried to a complete hemopoietic remission, the average count at the beginning of the therapy was 1,800,000 per c.mm., and the average count at the end of 6.6 weeks was 4,300,000. The most rapid remission was in Patient 6, whose blood increased from 1,200,000 per c.mm. to 5,600,000 per c.mm. in four and a half weeks on a daily dose of dried, defatted stomach tissue made from 281 gm. of fresh stomach.

Chart III shows the average increase in red blood cells per week

after effective dried stomach therapy. The slight increase during the first week, often absent in individual patients, would be misleading if used as a criterion of the effectiveness of the therapy, in the absence of adequate reticulocyte counts.

Some observations as to the origin of the hemopoietically active substances were made in hopes of throwing some light on the nature of the material. The desiccated muscle layer of the stomach defatted with acetone was fed in 30 gm. doses (representing 230 gm., of fresh muscle) daily to a patient with typical pernicious anemia with an initial red blood cell count of 1,070,000 per c.mm. No response was noted in ten days. Subsequently this patient had a perfect and typical response with whole stomach. The glandular

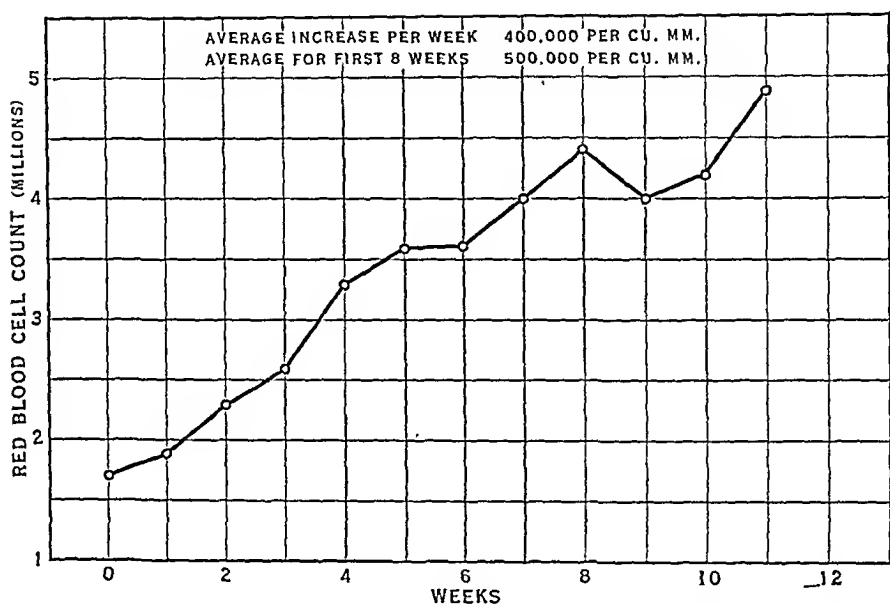


CHART III.—Average weekly red blood cell counts (19 patients) treated with dried defatted stomach.

portion of the mucosa, desiccated but not defatted, was fed in 30- and 60-gm. doses daily (representing 158 and 316 gm. of fresh mucosa) to another patient whose initial red blood cell count was 1,230,000 per c.mm. With 30 gm. daily there was a reticulocyte response to 6.8 per cent instead of the expected 27.5 per cent. With 60 gm. there was a secondary rise to 9.3 per cent. Subsequently this patient received whole stomach (28 gm. of desiccated stomach representing 240 gm. of the fresh organ) and had a very satisfactory increase of the reticulocytes to 36.6 per cent, in comparison to a calculated rise of 20 per cent. In 4 other patients fed mucosa, 3 gave no reticulocyte response at all, and 1 gave a questionable slight response.

These experiments suggest that the muscle layer probably does

not contain the hemopoietically active substance in free form and corroborates the clinical experience that meat is not effective in inducing a remission in pernicious anemia. Some of the hemopoietically active substance is present in the mucosa. The markedly increased activity when both are ground together while in the fresh state suggests that there is present in the mucosa an enzyme-like substance which acts on proteins and liberates the active principle. This is confirmatory evidence to the hypothesis of Castle.² The enzyme is absent in the muscle layer and so no active substance develops. Enough protein is present in the mucosa for the "enzyme" to liberate some of the substance. The work of Castle suggests that this "enzyme" or generating substance is absent in the stomachs of patients with pernicious anemia. His evidence is that it is excreted by the stomach, and the present work shows that it is in the mucosa from which it evidently originates.

Summary. Desiccated, defatted, whole stomach is effective in inducing and maintaining a hemopoietic remission in patients with pernicious anemia. Seven to 10 gm. of the dried substance daily, representing 50 to 67 gm. of the fresh organ have been found effective. A clinical dosage of 10 gm. for each million red blood cells deficit per cubic millimeter offers a wide margin of safety. The response is similar to that following liver extract, and the average increase in the number of red blood cells is about 500,000 per c.mm. per week during the first eight weeks.

REFERENCES.

1. Minot, George R., and Murphy, William P.: Treatment of Pernicious Anemia by a Special Diet, *J. Am. Med. Assn.*, 1926, 87, 470.
2. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, *Am. J. Med. Sci.*, 1929, 178, 748.
Castle, W. B., and Locke, E. A.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *J. Clin. Invest.*, 1928, 6, 3.
Castle, W. B., and Townsend, W. C.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, *Am. J. Med. Sci.*, 1929, 178, 764.
3. McCann, W. S.: Effect of Kidney on Blood Regeneration in Pernicious Anemia, *Proc. Soc. Exp. Biol. and Med.*, 1928, 25, 255.
4. Sturgis, Cyrus C., and Isaacs, Raphael: Desiccated Stomach in the Treatment of Pernicious Anemia, *J. Am. Med. Assn.*, 1929, 93, 747.
5. Conner, H. M.: The Treatment of Pernicious Anemia with Raw and Cooked Swine Stomach, *J. Am. Med. Assn.*, 1930, 94, 388.
6. Wilkinson, J. F.: Pernicious Anemia: Preliminary Report on the Results Obtained by Treatment with Certain Preparations of Stomach, *British Med. Jour.*, February 8, 1930, p. 236.
7. Riddle, Matthew C.: Personal communication; data to be published.

THE TREATMENT OF PERNICIOUS ANEMIA WITH AN EXTRACT OF FISH LIVER.

BY JOSEPH E. CONNERY, M.D.,

ASSISTANT PROFESSOR OF CLINICAL PATHOLOGY, NEW YORK UNIVERSITY; VISITING
PHYSICIAN TO BELLEVUE HOSPITAL, NEW YORK CITY.

(From the Department of Medicine, University and Bellevue Hospital Medical
College, New York University, and the Third (New York University) Medical
Division of Bellevue Hospital.)

WHIPPLE¹ established the fact, in animals rendered experimentally anemic by repeated bleedings, that of a number of foodstuffs studied to determine their hemoglobin regenerating power, mammalian and chicken liver and kidney were the most potent. Fish liver was found to be ineffective.

Minot and Murphy² showed that liver, when fed in adequate amounts to patients with pernicious anemia, induces a remission and that this remission can be sustained by a suitable maintenance dose. Cohn, Minot, Alles and Salter³ fractionated mammalian liver in an attempt to determine the nature of the active principle or principles. Porter⁴ prepared an active aqueous extract of liver. Castle⁵ demonstrated quite effectively that the feeding of the contents of the normal stomach after a meal of beef can induce a reticulocyte response in patients with pernicious anemia. Sturgis and Isaacs⁶ prepared a desiccated extract of hog stomach which was found to be potent.

In this paper we report the effect in pernicious anemia of an aqueous extract of the livers of cod, haddock and other members of the Gad. cal. family, from which the oil has been removed. Further process of preparation is essentially that used in making fraction G, as reported by Cohn, Minot, Alles and Salter.³

The 6 patients reported on in this series were typical cases of pernicious anemia of the Addisonian type. Daily reticulocyte counts, red cell counts, hemoglobin estimations and white cell counts were made. The physical condition of the patient permitting, a control period up to seven days was run. Where this was not possible, no patient was included in the study whose reticulocyte increase began in less than five days after treatment was started. Fish liver extract* was then administered, the daily dose usually being divided into halves. Each of these halves was then given with an equal volume of ice water by mouth. Meats of all kinds were excluded from the diet until the reticulocytes had reached their peak and returned to normal. During no phase of the study was liver or kidney included in the diet.

* This extract was prepared by the White Laboratories. In the paper it is also referred to as marine liver extract.

Plate I is composed of charts showing the reticulocyte curves of all 6 patients. The red cell, hemoglobin and white cell determinations were purposely omitted for the sake of clarity. The average number of days clapsing before the reticulocytes began to increase definitely in Cases I, II,* III, IV and VI was six. Case V had been irregularly and incompletely treated with whole mammalian liver before coming into the hospital. His reticulocytes showed a slight fluctuating increase, beginning shortly after treatment was instituted, but the definite upward trend did not occur until fifteen days of treatment had been followed. The subjective and objective improvement in all 6 patients was quite comparable to that seen in patients with pernicious anemia treated with adequate amounts of whole mammalian liver or of a liver fraction. Table I shows the hemoglobin in grams and per cent (Newcomer) and the level of the red cells at the end of two weeks', one month's and two months' treatment.

There follow brief protocols of the 6 cases:

HEMOGLOBIN IN GRAMS AND PER CENT AND THE LEVEL OF THE RED CELLS AT THE END OF TREATMENT FOR SPECIFIED TIME.

Case.	Two weeks.			One month.			Two months.		
	Hemoglobin.		R.b.c.	Hemoglobin.		R.b.c.	Hemoglobin.		R.b.c.
	Grams.	Per cent.		Grams.	Per cent.		Grams.	Per cent.	
I . .	11.1	65.0	2.7						
II . .	5.5	32.7	1.2	10.9	64.4	3.1	13.6	80.4	3.7
III . .	9.8	72.0	3.2	10.0	73.0	4.1	10.3	75.0	5.4
IV . .	6.1	45.0	2.6	8.7	63.0	3.6	8.9	65.0	4.1
V . .	6.1	45.0	1.1	9.8	72.0	2.6	11.7	86.0	4.3
VI . .	6.8	50.0	2.1	7.5	55.0	2.2	8.3	61.0	3.4

Case Protocols. CASE I.—B. R., female, white, aged seventy years, first hospitalization, had an initial red cell count of 1,990,000, initial hemoglobin 44 per cent or 7.4G (Newcomer), initial reticulocytes 0.7 per cent, and initial white cell count 3400.

Marine liver extract (White) (90-cc. doses) was begun on the fifth day of hospitalization.

Reticulocyte increase began on the fifth day of treatment, and there ensued marked subjective and objective improvement (Chart I).

CASE II.—C. H., male, white, aged fifty-four years, first hospitalization, neurological involvement not marked, had an initial red cell count of 1,090,000, initial hemoglobin 24.8 per cent or 4.2G (Newcomer), initial color index 1.24, initial reticulocytes 2.7 per cent and an initial white cell count of 2,400.

Marine liver extract (White) (90-cc. doses) was begun on the fourth day of hospitalization.

Reticulocyte increase began on the fifth day of treatment, and then occurred marked subjective and objective improvement (Chart II).

CASE III.—M. B., male, white, aged fifty-five years, first hospitalization, neurological involvement, marked subacute combined sclerosis; had an initial red cell count of 2,180,000, initial hemoglobin 69 per cent or 9.4G (Dare), initial color index, 1.64, initial reticulocytes 1.7 per cent and an initial white cell count of 7200.

* Case II: This patient was followed on the Second (Cornell) Medical Division of Bellevue Hospital through the courtesy of Dr. Eugene F. DuBois.

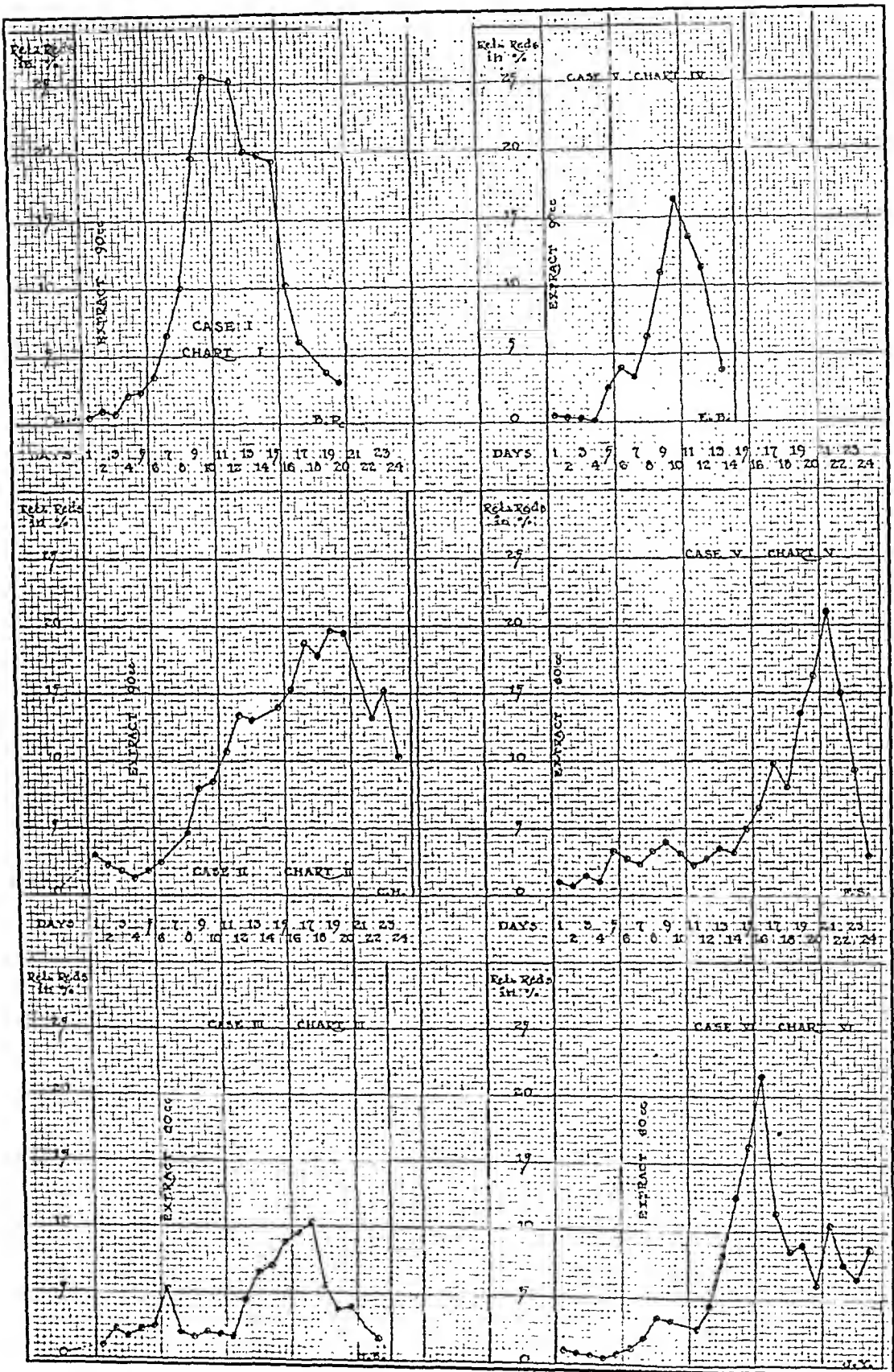


PLATE I.—Reticulocyte curves on all six patients.

Marine liver extract (White) (60-cc. doses) was begun on the eighth day of hospitalization.

Reticulocyte increase began on the seventh day of treatment, and the patient experienced moderate subjective and objective improvement, but very slight neurologic improvement (Chart III).

CASE IV.—E. B., female, white, aged sixty-nine years, first hospitalization, slight neurologic involvement, had an initial red cell count of 1,610,000, initial hemoglobin 35 per cent or 4.8G (Dare), initial color index 1.09, initial reticulocytes 1 per cent, and an initial white cell count of 3000.

Marine liver extract (White) (90-cc. doses) was begun on the fourth day of hospitalization.

Reticulocyte increase began on the sixth day of treatment, and there occurred marked subjective and objective improvement (Chart IV).

CASE V.—F. S., male, white, aged thirty-eight years, first hospitalization, with slight neurological involvement, had an initial red cell count of 1,240,000, initial hemoglobin 33 per cent or 4.5G (Dare), initial color index 1.3 per cent, initial reticulocytes 1.7 per cent, and an initial white cell count of 3000.

Marine liver extract (White) (60-cc. doses) was begun on the sixth day of hospitalization.

Reticulocyte increase began on the ninth day of treatment, and there occurred marked subjective and objective improvement (Chart V).

CASE VI.—J. Y., male, white, aged sixty-nine years, first hospitalization, only slight neurologic involvement, had an initial red cell count of 1,030,000, initial hemoglobin 46 per cent or 6.3G (Dare), initial color index 2.3, initial reticulocytes 0.6 per cent, and an initial white cell count of 1800.

Marine liver extract (White) (60-cc. doses) was begun on the seventh day of hospitalization.

Reticulocyte increase began on the sixth day of treatment, and there occurred marked subjective and objective improvement (Chart VI).

Comment. An aqueous extract of fish liver administered in adequate dosage to patients suffering with pernicious anemia can induce a reticulocyte response and an increase in the red cells and hemoglobin. Subjective and objective improvement follows and is comparable to that seen in patients with pernicious anemia treated with whole mammalian liver or with adequate amounts of potent liver fraction. Another source of the principle or principles capable of inducing a remission in pernicious anemia is demonstrated.

BIBLIOGRAPHY.

1. Whipple, G. H.: Experimental Anemias: Diet Factors and Related Pathologic Changes of Human Anemias, *J. Am. Med. Assn.*, 1928, **91**, 863.
2. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Specific Diet, *J. Am. Med. Assn.*, 1926, **87**, 470; A Diet Rich in Liver in the Treatment of Pernicious Anemia, *J. Am. Med. Assn.*, 1927, **89**, 759.
3. Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia, *J. Biol. Chem.*, 1928, **77**, 325.
4. Porter, W. B., Williams, J. P., Forbes, J. C., and Irving, H.: Aqueous Extract of Liver: Development and Use in Treatment of Pernicious Anemia, *J. Am. Med. Assn.*, 1929, **93**, 176.
5. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Am. J. Med. Sci.*, 1929, **178**, 748.
6. Sturgis, C. C., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, *J. Am. Med. Assn.*, 1929, **93**, 747.

MITOSIS IN MYELOBLASTS IN PERIPHERAL BLOOD.

BY WILLIAM A. GROAT, B.S., M.D.,

PROFESSOR OF CLINICAL PATHOLOGY, COLLEGE OF MEDICINE, SYRACUSE UNIVERSITY,
SYRACUSE, N. Y.

(From Department of Clinical Pathology, College of Medicine, Syracuse University.)

THE following case is discussed because of the unusual blood findings in one smear only of a daily series covering a period of nearly three weeks.

Case Report.—A Jewish woman, aged eighteen years, entered the Hospital of the Good Shepherd early in the year 1909.* There was high temperature; enormously enlarged liver and spleen, petechial hemorrhages, foul, ulcerated mouth and fauces, bleeding from the gums which were soft and spongy, and the blood picture of acute leukemia. The red count from day to day varied from slightly above to slightly below 1,000,000 cells. The white count likewise hovered around the million mark, often slightly exceeding the red. The vastly predominating white cell, as shown in the accompanying photomicrographs, was one which most authorities would call a myeloblast. Oxidase and supravital staining methods were not available at that time. There were to be found at all times typical myelocytes in numbers varying from 4 per cent to 10 per cent, which, in so large a total, means as high as 100,000 per c.mm. Numerous erythroblasts, some in mitosis, were in the daily smears. Occasional polymorphonuclear leukocytes and lymphocytes were present, but fields were always dominated by cells of primitive myeloblastic type. On the sixteenth day of her stay in the hospital I obtained the smear in which was found the entire series of mitotic figures shown. It is solely this feature which I now present.

The mitotic series runs from early spireme through prophase, metaphase, anaphase and telephase in the highly primitive proliferating myeloblastic type of cell which characterizes this case. The nuclei of these cells stain a rich reddish violet, the cytoplasm clear bright blue. (Wright's stain, 1100 \times .) In none of these mitotic cells was there any granular appearance of cytoplasm or any tinge of pink. A few mitotic figures from the same smear, in cells which from morphology and staining affinity I believe to be erythroblasts, are shown for comparison.

If we accept the work of Ellermann,¹ the polar angle of the chromosomes in the cells of the principal series supports the contention they are myeloblasts; not lymphoblasts or erythroblasts. Using bone marrow, spleen, lymph gland and infiltration of wall of

* Only recently have I had the high order of photomicrographic assistance necessary for collecting and consolidating this particular series of mitotic figures for presentation in this manner.

the pelvis of the kidney, Ellermann believed he had added something definite for *differentiation* between myeloblasts and lymphoblasts through measurement of the angle chromosomes made with the spindle in mitotic figures. Measuring at least forty angles in each case, first, from drawings, and later, with a goniometer ocular, he reports erythroblasts with angles always very close to 20 degrees, myeloblasts with a definitely shorter, broader spindle and angles of 70 degrees. Later, studying 2 cases of acute leukemia,² he makes further contribution on the differentiation of myelogenous and lymphatic leukemia, giving average angles for erythroblasts of 21 degrees, lymphoblasts 40 degrees, myeloblasts 69 degrees. The angles in this case were very close to 70 degrees.

Sabin, Austrian, Cunningham and Doan³ state that in the myeloblastic leukemic blood studied with the then new supravital staining technique a striking feature was the amount of amitotic division of myeloblasts in the blood stream. They mention finding in fixed smear a cell in mitosis but none in their living preparations. It is not stated what type of cell they found in mitotic division in the fixed smear.

With this possible exception, I find no reference in literature to mitotic division of myeloid or lymphoid cells in circulating blood.

In marrow sections in myeloblastic leukemia, mitotic figures are of course found. Active mitotic division in leukemic cells going on in the peripheral blood is another and a striking indication of similarity or association between the leukemic states and the malignancies.

Summary and Conclusion. 1. Photomicrographs of a series of leukoblastic cells in mitotic division are shown.

2. These cells from circulating blood of a case of acute myeloblastic leukemia form a complete series of mitotic figures from early prophase through metaphase and anaphase to latest telephase.

3. The angle the chromosomes bear to the spindle can be measured approximately in these photomicrographs and is found to be very close to 70 degrees, agreeing with the goniometric measurements made by Ellermann of myeloblasts in tissue sections.

4. Mitotic division in leukemic cells in peripheral blood is added evidence of possible relationship between leukemia and malignancy.

BIBLIOGRAPHY.

1. Ellermann, F.: *Hæmatol. Arch.*, 1923, **28**, 207.
2. Ellermann, F.: *Ibid.*, 1924, **30**, 1.
3. Sabin, Austrian, Cunningham and Doan: *J. Exper. Med.*, 1924, **40**, 845.

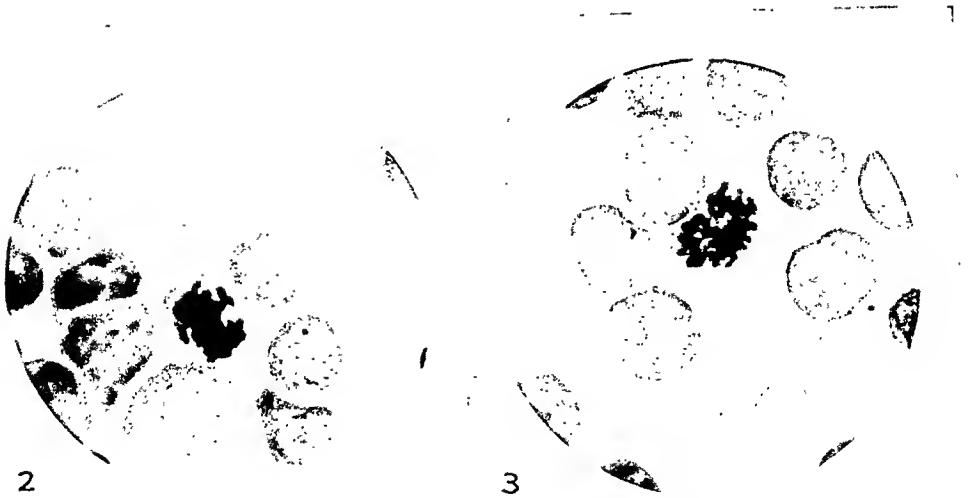
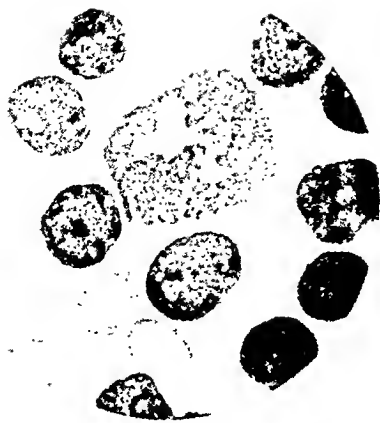
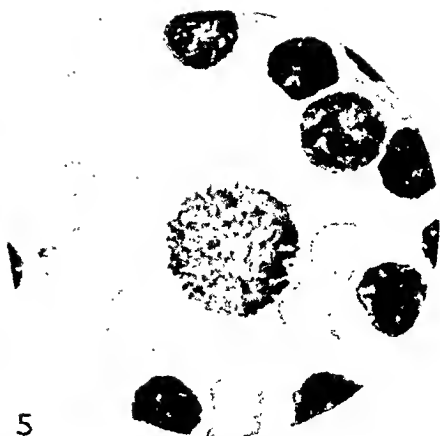


FIG. 1.—General view of the blood of the case reported as acute myeloblastic leukemia. Photomicrograph, magnification $\times 1100$. All mitotic figures hereafter shown are from the same smear as above, and $\times 1100$. (Slightly reduced in reproduction.)
 FIGS. 2 and 3.—Mitotic erythroblasts for comparison with mitotic myeloblasts which follow (Figs. 4 to 19).

4



5



6



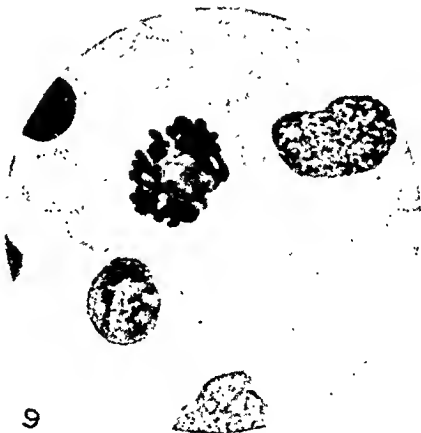
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MYELOBLASTS IN MITOTIC DIVISION.

PROPHASE.

FIG. 4.—Early spireme.

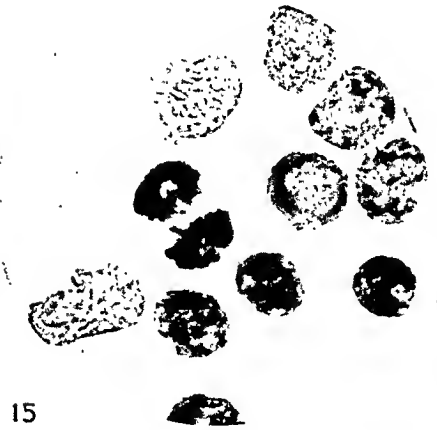
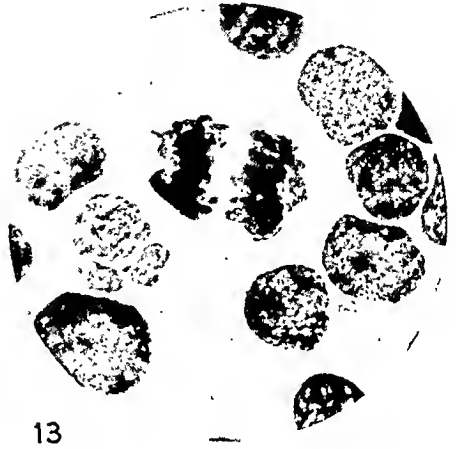
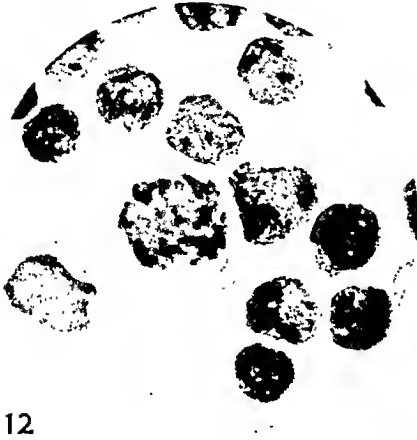
FIG. 5.—Beginning linear arrangement of spireme.

FIG. 6.—Beginning shortening of spireme.

FIG. 7.—Early suggestion of monaster

FIG. 8.—True monaster, polar view.

FIG. 9.—True monaster, oblique view.



MYELOBLASTS IN MITOTIC DIVISION.

METAPHASE.

FIG. 10.—Chromosomes arranged on equatorial plate, slightly oblique view.

FIG. 11.—Definite separation.

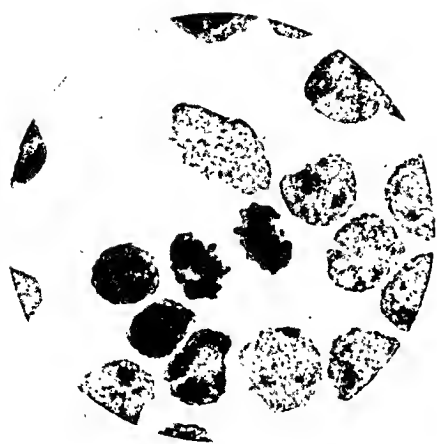
ANAPHASE.

FIG. 12.—Beginning anaphase, oblique view.

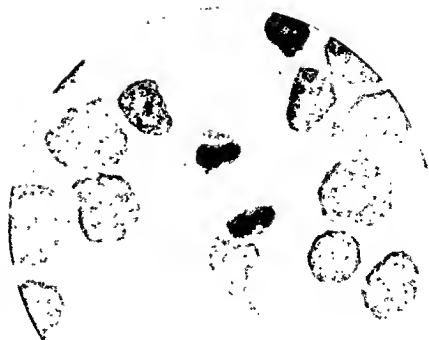
FIG. 13.—Later anaphase side view.

FIG. 14.—Early concentration at both poles.

FIG. 15.—Late polar concentration.



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TELEPHASE.

FIG. 16.—Early telephase. Slight equatorial constriction of cytoplasm.

FIG. 17.—Definite equatorial separation of cytoplasm and bipolar concentration of chromosomes.

FIG. 18.—Well-advanced separation. Cytoplasmic connection reduced to narrow isthmus permitting rotation.

FIG. 19.—Final separation.

RADIATION THERAPY OF POLYCYTHEMIA VERA.

BY GEORGE T. PACK, M.D.,

AND

LLOYD F. CRAVER, M.D.,

NEW YORK.

(From the Memorial Hospital, New York City.)

ERYTHREMIA is a symptom complex characterized by cyanosis, polycythemia and splenic enlargement. Vaquez, in 1892, first established this disease as an entity, hence the eponym, "Vaquez's disease."

The following classification of polycythemia is given to indicate the proper selection of cases for radiation therapy:

(a) Functional, relative or compensatory polycythemia. This variety is generally physiologic and temporary. It is exemplified by the polycythemias of high altitudes, fright, dehydration, and so forth. Irradiation is unnecessary.

(b) Erythremia. Essential or absolute polycythemia. Polycythemia vera.

1. *Ayerza's disease*—"cardiacos negros," is a form of the disease characterized by sclerosis of the pulmonary artery, enlargement of the right heart, cyanosis, polycythemia, dyspnea, cough and hemoptysis. The nature of the cardiopulmonic lesions accounts for the inefficacy of radiation therapy.

2. *Polycythemia hypertonica of Gaisböck* presents the clinical picture of arteriosclerosis, hypertension, nephritis and polycythemia. Irradiation as a palliative measure is of some benefit in banishing the distressing symptoms of plethora, but does not prolong life.

3. *Polycythemia with splenomegaly* is the common sort, originally described by Vaquez. Irradiation is the mode of treatment *par excellence*.

The rationale of radiation therapy for this disease is based on the character of the pathology. The principal mechanism in the maintenance of the blood picture seems to be a chronic overproduction of red blood cells rather than a delayed destruction or prolonged life of these cells. Inasmuch as the red blood cells are probably destroyed as rapidly as in a normal individual, the continued high erythrocyte count is due to an abnormal and increased activity of the blood-forming organs. The mode of the normal physiologic regulation of the number of blood cells per unit volume of blood is even less well known than the mechanism of the normal regulation of body temperature at a constancy of 98.6° F. When this balance between production and destruction of erythrocytes is disturbed in polycythemia it is assumed that the normal rate of destruction is

insufficient to counteract the increased rate of production of these cells. The stimulus or cause of this condition is unknown, but the chief seat of action is in the bone marrow, where there is definite anatomic evidence of increased erythroblastic activity. Although it remains impossible to eradicate the cause of this disease, the logical procedure in treatment would be an attempt to inhibit this excessive erythropoiesis.

The erythroblastic and to a less extent the leukoblastic tissues of the bone marrow are hyperplastic. Yellow marrow is replaced by red marrow to simulate the character and distribution of the marrow in children. The enlarged spleen is markedly congested, but does not show any evidence of erythropoiesis; therefore, its increment can be attributed to secondary changes induced by the increase in red blood cells. The splenic pulp oftentimes shows a slight myeloid transformation, which may account for the occasional concomitant leukocytosis or slight leukemic state.

A clinical analogue of erythremia is myelogenous leukemia. Their relationship is apparent because they occur during the same age periods; they pursue the same chronic progressive and fatal evolution and certain transitional forms of the disease exist. The experience of the Memorial Hospital indicates that irradiation is the most satisfactory means of treating myelogenous leukemia; therefore, it seems reasonable to apply this same therapeutic measure in cases of polycythemia vera.

Osler asserted that his patients had never been benefited by Roentgen ray treatments. Stengel, in 1907, was the first to advocate irradiation of the bone marrow for this disease. Pagniez Le Sourd and Beaujard, in 1913, in the *Archives des maladies du cœur*, first reported a series of treatments of the spleen by irradiation in which they obtained a diminution in splenic volume, an amelioration of symptoms and a reduction in the number of erythrocytes by 500,000 per c.mm. of blood. However, it was a Swiss physician, Ludin, of the University of Basle, who, in 1916, first successfully irradiated the skeletal long bones of an erythremic patient with a resultant change in the erythrocyte count from 8,000,000 to 4,800,000 cells; the blood remained normal for two and a half years. In 1918 Hurwitz and Falconer employed Roentgen rays and benzol in the treatment of a patient with polycythemia vera: the irradiation was given to the spleen only, but the number of erythrocytes diminished from 12,400,000 to 4,500,000 per c.mm. of blood during the two years of observation. These authors asserted that benzol rendered the erythropoietic tissues less resistant to the action of radiation. Rydgaard, in 1921, treated the spleen of a polycythemic patient with Roentgen rays; there was an apparent cure for eighteen months, at the time of his report. Bécclère applied the Roentgen rays over the skeletal bones of 2 patients with polycythemia vera in 1922; the erythrocytes in one instance were reduced from 9,300,000 to

6,600,000 per c.mm. of blood and in the second instance from 12,640,000 to 8,000,000 erythrocytes. In 1923 Stolkind similarly applied Roentgen rays over the skeletal bones of 2 erythremic patients with comparable results; in one patient the red cell count was reduced from 9,500,000 to 7,700,000 in two weeks and in the second patient from 8,300,000 to 5,600,000 per c.mm. of blood in ten weeks.

In our opinion, the physical agents, that is, radium and Roentgen rays, are superior to chemical agents, such as benzol and phenylhydrazin in the treatment of those diseases characterized chiefly by an excessive activity of bone marrow. The results though temporary are of longer duration than occur with benzol or phenylhydrazin. Splenectomy is contraindicated in erythremia; indeed, it is essential that the spleen be intact and functional. Venesection affords symptomatic relief and is frequently used, but possibly may dangerously stimulate the bone marrow to increased activity.

Marrow cells are radio-sensitive. The law of Bergonie and Tribondeau purports that the degree of radio-sensitivity of any tissue is directly proportional to its rate of mitosis; therefore, the hyperplastic marrow in erythremia should be markedly radio-sensitive. Even the normal bone marrow is quite susceptible to the influence of radiant energy, as shown by the development of the so-called radiation anemia after heavy Roentgen ray treatments of multiple bone tumors. The primary tumors of the bone marrow, namely, the multiple myeloma and the endothelial myeloma of Ewing, are very radio-sensitive neoplasms. The leukopoietic tissues are less resistant to the action of the Roentgen rays and gamma rays of radium than are the tissues concerned with the formation of red blood cells; indeed, the circulating white blood cells may diminish rapidly in number while the number of erythrocytes is only slightly influenced, unless careful dosage is observed.

Bottner and Pendergrass independently urged the application of so-called stimulative or irritative doses of radiation to the spleen on the presumption that such treatment facilitates or hastens the destruction of erythrocytes by the spleen. In our cases (Cases III and IV), treated in 1917 and 1920 in Memorial Hospital, light insufficient radiation was administered to each splenic area with little demonstrable effect. We seriously doubt the stimulative quality of any irradiation in this respect and have a second reason for future discontinuation of irradiation of the spleen because of the absence of erythropoiesis in this organ. Possibly such treatment induces hemolysis, which may account for the slight diminution in the red cell count.

Now, if the locus of this disease is primarily in the bone marrow, as indicated by the hyperplasia of this tissue, then the proper treatment must be directed to the bone marrow. Sufficient irradiation must be given to inhibit or depress but not to destroy erythropoiesis.

The amount of irradiation depends on the severity of the illness, one criterion of which is the degree of the polycythemia. The treatment is carefully controlled by observing the condition of the patient and the changes in the number of leukocytes. Although both short and long bones are subjected to irradiation, the long bones receive the most attention, particularly those which are painful. The entire skeleton may be irradiated, although the head is spared in order to avoid alopecia; the pelvic bones in young women and men are not treated because of the possible damage to the gonads. Exact dosage is essential. For a series of treatments, three to six exposures a week are employed until the cycle is complete. Sometimes three series of treatments are necessary, which may be given at intervals of three to six months, depending on the response of the patient to treatment and the maintenance of a normal erythrocyte count.

Irradiation in polycythemia seems not to cause the disagreeable toxemia which frequently follows this treatment of myelogenous leukemia. Furthermore, it is agreed that irradiation prevents the formation of new erythrocytes rather than increasing the rate of hemolysis of red blood cells already formed. The patients obtain quick relief by the cessation of bone pains. The headache, vertigo, cyanosis and dyspnea, so common in this disease and provoked by the existent plethora, are appreciably diminished by this form of therapy. Radiation therapy of erythremia lowers the blood pressure, improves the general health and prolongs life, but is incapable of preventing the ultimate fatal termination of this disease. The intensity, dosage and interval between treatments should be carefully controlled in order to avoid the possible danger of radiation osteitis.

Case Reports. CASE I.—S. M., a Rumanian Jewess, aged fifty years, was admitted to the Memorial Hospital on August 30, 1928, with the chief complaints of headache, vomiting and loss of weight. Her mother, aged sixty-five years died of diabetes; her father, aged seventy-six died of paralysis. Her habits were good. Her maximum weight was 195 pounds in January, 1925; in July, 1926 she weighed 135 pounds; on admission her weight was 124 pounds.

Past History. Menses began at age of thirteen; they occurred regularly every thirty days and lasted eight days. She had 4 children, aged thirty, twenty-eight, twenty-five and nineteen years. She had 3 induced abortions in 1912, 1920 and 1921. In January and February, 1928, there was profuse menorrhagia of ten days' duration. She had recently entered the menopause; her last menstrual period was on May 20, 1928.

Present Illness. The onset was indefinite and insidious. The patient was always ruddy in complexion. She attributes the cause to a rubber corset which she wore as a treatment for obesity in February, 1925. This reducing measure induced profuse perspiration, asthenia and headache. Another possible contributing factor began twenty-six years previously when she was four months pregnant, namely, the spontaneous rupture of a large varicose vein on her leg with the resultant loss of a pint of blood; since which episode, the veins have ruptured almost yearly with the loss of two or three cupfuls of blood.

Supraorbital and later occipital headaches began in February, 1925, and have occurred every one to four weeks, lasting for twenty-four hours. With the headaches she has had a feeling of suffocation, substernal fullness and nausea. She has worn glasses for three and a half years; her vision has been progressively failing and she has had binocular diplopia several times and complains of "spots before her eyes." She fatigues readily and has become quite weak; complains of a throbbing in her head; has had palpitation and heart consciousness; was first aware of the enlargement of her spleen in June 1926 and since this time it has gradually and painlessly increased in size.

A summary of her pertinent symptoms is as follows: headaches, nausea, throbbing in head, diplopia, palpitation, fatigue, loss of weight, constipation, suffocation, and fullness in chest.

Previous Therapy. Her red blood-cell count had been 12,000,000 per c.mm. For two years she took phenylhydrazin in capsules in an attempt to diminish this count. In July 1926, 3 pints of blood were drawn by phlebotomy; in August 1926, 1 pint of blood, and in August 1928 another pint of blood were removed by phlebotomy.

Physical Examination. The patient was a thin, middle-aged woman, whose ruddy countenance seemed to contradict the presence of illness. Her face, neck and shoulders were congested, not blue but red predominating. Her appearance seemed preapoplectic. Her hands, nipples and superficial parts of the breasts were of the same color. Blanching by finger pressure disappeared slowly. The mucous membranes of the eyelids, nose, mouth and vagina were livid.

The conjunctival vessels were greatly dilated. On ophthalmoscopic examination the disk of the right fundus was somewhat engorged, although distinct in contour; an inferior vein was quite tortuous. There was no evidence of retinal hemorrhage. There was some pyorrhea as well as caries of the lower teeth. The lungs were normal. The first mitral sound was somewhat prolonged and slightly murmurous, probably a hemic murmur produced by the plethora. The liver was not tender, but extended three finger-breadths below the costal margin. The spleen was movable and nontender; it extended to the midline of the epigastrium, within 2.5 cm. of the umbilicus and 14 cm. below the costal margin in the left midclavicular line. Vaginal examination revealed a chronic catarrhal endocervicitis and a first degree retroflexion of the body of the uterus. Her reflexes were normal. The blood pressure was 180 systolic and 70 diastolic; the presence of a splenomegaly and high blood pressure is unusual, as in most erythremias, the one of these conditions predominates to the exclusion of the other.

A radiograph of the chest on August 31, 1928 showed considerable peribronchial infiltration of undetermined nature and origin. A teleroentgenogram of the heart on September 11, 1928 showed a normal ratio (14 systolic and 32 diastolic) between the transverse diameters of the heart and chest.

Irradiation. All treatments were by the Roentgen rays. In September 1928, four treatments were given to the spleen. Cycles of treatments were given to the upper, middle and lower spine, both tibias and sternum in November 1928, May 1929, August 1929 and April 1930. In May 1930, both forearms, humeri and right and left pelvis were irradiated. In the first four treatments, 135 kv., 5 mm. Al. filter, 37.5 target skin distance, and 4 ma. current for twelve minutes were used, the remaining doses used 135 and 140 kv., 4 mm. Al. filter and 30 cm. distance.

Course. In September 1928, four of her decayed teeth were extracted; continuous bleeding occurred during the next twenty-four hours, necessitating packing and suturing. By October 1928, the patient had gained 8 pounds in weight and the spleen was smaller. In December 1928, her blood pressure was 228 systolic and 110 diastolic. In July 1929, the spleen was

614 PACK, CRAVER: RADIATION THERAPY OF POLYCYTHÉMIA VERA.

less than a finger-breadth below the costal margin. In October 1929, she had a hemorrhage from the varicose veins on her right leg, losing $\frac{3}{4}$ pint of blood. In November 1929, Dr. Treves injected this varicose vein with 1 cc. of 40 per cent sodium salicylate. In February 1930, the patient stated that she felt very well; her spleen was small, her face less flushed than previously.

TABLE I.—LABORATORY REPORTS.

8-30-1928. Wassermann test: Negative.
 9-1-1928. Blood sugar: 125 mg. per 100 cc. of blood.
 9-3-1928. Bleeding time (Duke method). Two tests: Five and five-tenths and six minutes.
 Normal: Three minutes.
 9-3-1928. Coagulation time of blood (Brooks method): Nine to nine and three-quarters minutes.
 9-3-1928. Fragility test for red cells: Beginning hemolysis at 0.44 per cent NaCl; complete hemolysis at 0.32 per cent NaCl.
 9-3-1928. Test for bile in blood serum (Gmelin): Negative.
 9-6-1928. Blood calcium: 14.6 mg. per 100 cc. of blood.
 9-6-1928. Blood urea nitrogen: 18.0 mg. per 100 cc. of blood.
 9-6-1928. Blood uric acid: 4.3 mg. per 100 cc. of blood.
 Creatinine: 1.4 mg. per 100 cc. of blood.
 9-6-1928. Reticulocytes: $2\frac{1}{2}$ per cent (500 counted cells).
 9-5-1928. Phenolsulphonphthalein test: First hour, 80 per cent; second hour, 10 per cent; total, 90 per cent. Intravenous method.

	Hemo- globin, per cent.	Red blood cells in mil- lions.	White blood cells in thou- sands.	Differential count in per cent.						Special.
				Neut.	Large lymph.	Small lymph.	Trans.	Eosin.	Baso.	
1928.	110	12.00	14.4	73	4	20	2	1	6	Polychromato- philia—2
7-28	85	6.32	8.2	66	2	19	2	5	1	
8-30	90	6.00	8.2	85	9	19	1	1	1	
9-15	90	6.30	8.2	81	5	2	6	3	3	
10-4	90	6.40	8.4	82	6	4	2	1	1	
10-18	90	7.43	8.4	83	4	6	3	1	3	
11-1	90	6.32	8.4	83	15	30	..	2	2	
12-6	95	5.32	8.0	62	7	19	1	4	3	
1929.	95	7.22	8.0	69	6	10	1	4	3	
1-3	90	5.12	7.6	76	12	7	1	4	3	
1-24	90	4.64	6.2	71	2	14	1	1	3	4
3-28	90	5.60	6.9	80	3	20	3	3	1	1
5-2	85	7.84	7.6	69	3	8	6	3	2	2
6-10	90	8.20	6.6	84	6	6	4	4	2	2
7-1	85	9.00	6.6	80	8	8	4	..	2	2
8-12	85	5.52	7.4	80	3	10	3	3	4	1
10-4	85	7.56	6.2	78	3	5	18	1	3	1
12-2	85	6.72	9.4	83	3	3	5	..	3	..
12-30	85	7.84	8.2	85	5	18
1930.	85	11.44	5.3	72
1-13	85	6.22
3-31	85
5-3	85

Comment. The polycythemia was well controlled by the irradiation of spine, tibias and sternum. After an interval of six months, during which the patient received no Roentgen-ray treatment, the red blood count increased to more than 11,000,000 per c.mm. of blood. The injection treatment of the varicose veins was successful; no further hemorrhage occurred from this source; we do not attribute the increased cell count to a cessation of these intermittent hemorrhages, but to a return to the former pathologic hematopoietic activity. This has again responded well to irradiation. At first we spared the humerus and femur from irradiation; now they may be subjected to irradiation, in order to spare the previously irradiated bones from the dangers of overdosage.

CASE II.—R. F., a Hungarian woman, married, aged fifty-nine years, reported to the Memorial Hospital on June 14, 1917, with the chief complaint of enlargement of her abdomen. Her mother, aged seventy-five

years, died of general anasarca. Her father died of unknown cause at forty-nine years of age. Her normal weight was 160 pounds.

Past History. Menstruation had always been irregular. She entered the menopause when fifty-one years of age. In 1910 she had pneumonia.

Present Illness. Five years previously, in 1912, the patient noticed intermittent pain in the left hypochondrium. In 1915 this pain became severe and the patient for the first time felt an unnatural mass in this region. She had intermittent vomiting and almost constant anorexia. She gradually became weaker and by the time of admission had lost 60 pounds in weight.

Physical Examination. The patient was an emaciated, elderly woman with dry red skin and mucous membranes. She had severe pyorrhea. Her lungs were normal but her heart was enlarged and arrhythmic. The spleen was very large; it extended to the brim of the pelvis on the left side and 2 inches to the right of the median line in the region of the umbilicus. It was impossible at this time to ascertain the condition of the liver because of the tenseness of the abdominal wall. A radiograph of the chest showed considerable infiltration about the hila.

TABLE II.—LABORATORY REPORTS.

	Hemo- globin, per cent.	Red blood cells in mil- lions.	White blood cells in thou- sands.	Differential count in per cent.						Special.
				Neut.	Large lymph.	Small lymph.	Myel.	Eosin.	Baso.	
1917.										
6-15 . . .	105	7.87	57.9	63	23	..	3	8	3	
6-23 . . .	99	4.98	37.0	84	..	7	3	4	2	
6-26 . . .	99	6.51	16.5	82	..	1	8	7	2	
6-28 . . .	96	7.90	15.7	87	..	8	1	3	1	
7-2 . . .	105	8.00	19.0	85	..	9	..	4	2	
7-10 . . .	96	5.60	20.8	85	..	9	..	4	2	
7-19 . . .	106	6.92	19.0	71	4	19	1	4	1	
8-7 . . .	95	6.80	14.0	71	5	17	4	2	2	
8-12 . . .	90	5.67	22.4	78	..	18	1	..	1	2—megaloblasts.
11-15 . . .	107	7.24	38.0	84	..	5	4	7—normoblasts.
1918.										
1-2 . . .	100	5.36	57.0	85	..	2	5	2	..	6—normoblasts.
2-23 . . .	98	4.96	16.6	85	3	7	..	3	1	1—normoblasts.
6-14 . . .	110	6.80	14.4	84	5	6	2	2	1	
6-24 . . .	105	5.48	13.4	86	..	7	..	4	3	
7-1 . . .	105	5.80	9.8	87	1	4	..	7	1	
12-20 . . .	100	6.08	23.6	45	4	12	18	5	7	8—normoblasts.
1919.										
1-3 . . .	100	6.00	10.0	69	5	4	10	..	1	1—normoblasts.
1-23 . . .	90	5.86	4.5	88	6	4	2	
6-27 . . .	85	7.12	14.0	73	..	16	4	6	..	1—normoblasts.

Radium Therapy.

	Amount of radon in milli- curies.	Filter.	Distance in cm.	Time in hours.	Appli- cator.	Dosage in millieurie hours.	Region.
1917.							
6-20 . . .	840	2 mm. Pb	10	14	Pack	11,760	Spleen.
6-21 . . .	720	2 mm. Pb	10	14	Pack	10,080	Spleen.
11-16 . . .	420	2 mm. Pb	21	16	Plaque	6,720	Spleen.
1918.							
2-20 . . .	1475	2 mm. Pb	6	(a) 6	Pack	14,700	Spleen, posterior.
6-21 . . .	720	1 mm. Ag	..	(b) 41	Pack	Total	Spleen, anterior.
6-25 . . .	835	"	4	3	Tray	2,160	Spleen, Area No. 1.
6-26 . . .	700	"	4	2	Tray	1,670	Spleen, Area No. 2.
6-26 . . .	1131	"	4	21	Tray	1,750	Spleen, Area No. 3.
12-29 . . .	1635	"	6	6	Tray	2,260	Spleen, Area No. 4.
					Pack	10,000	Spleen.

Roentgen Ray Treatment. Cycles of Roentgen ray treatments were given to both lower legs, both thighs, both forearms, both upper arms and right and left, upper and lower chest anteriorly and posteriorly in June 1918, January 1919 and July 1919. In all, 33 treatments were given. In all treatments, the following factors were employed; kilovoltage, 120; filter of 4 mm. Al.; milliamperage, 7; target skin distance, 20 cm.; and time, five minutes.

Course. On August 7, 1917, the patient felt very well and stated that she was able to do her own housework. At this time, the spleen extended only 2 finger breadths' above the umbilicus on the left side. By July 19, 1917, her weight had increased to 114 pounds; the liver could be palpated at the level of the umbilicus on the right side. In December 1917, the spleen was only slightly below the left costal margin. In June 1918, the patient's improvement stopped; shortly afterward, the spleen was 1 cm. to the right of the midline and 5 cm. below the level of the umbilicus on the left side; the liver was also greatly enlarged. The patient weighed 121 pounds. After treatment the patient improved greatly by July 1918. This improvement continued until December 1918, when she experienced pain in various regions of her body; she had profuse perspiration, painful urination, anorexia and asthenia. The spleen occupied two-third of her abdomen. She received immediate vigorous treatment over the long bones and remained well for another year. In December 1919, her condition was better than at any time since admission to this hospital. She was lost to observation for a time. The next relapse was fatal and the patient died in December 1920.

CASE III.—S. R., a married white woman, aged forty-four years, reported to the Memorial Hospital on March 12, 1920. Her father died aged sixty-three years, of intraoral cancer; her mother died aged seventy-eight years, of heart disease.

Past History. Menses were established at age of fourteen years; she had two children, one in 1906, another in 1912. Menopause occurred one year before admission to the hospital, at age of forty-three years. In 1913 she had diphtheria; in 1919 she had pneumonia. In July 1917, an appendicectomy and uterine suspension were performed.

Present Illness. In March 1919, her ankles became markedly swollen and she had pain in her legs so that locomotion was difficult. In July her physician made a diagnosis of "thyroid disease" and ordered her to bed. At this time she had severe backache (lumbago) and two weeks later developed pneumonia. Her face had been intensely florid for over a year, and for two years she had been aware of an unnatural fullness of her abdomen.

Physical Examination. The patient was a well-nourished, small woman, who weighed 110 pounds. Her face was quite florid and her pupils were dilated. Moist râles were heard over the lower lobe of the left lung. The heart was slightly enlarged; an apical systolic murmur was transmitted to the left axilla. The skin of the abdomen showed a bluish discoloration. The abdomen was so distended with ascitic fluid that no organ could be palpated. Both legs were bright red in color and edematous. A radiograph of the chest showed an elevation of the diaphragm on the left side and a displacement of the heart to the right.

A blood count was made on October 18, 1919.—Red blood cells, 8,500,000 per c.mm.; white blood cells, 12,000 per c.mm. Differential white count: Polymorphonuclear leukocytes (neutrophilic), 84.8 per cent; small lymphocytes, 5.5 per cent; large lymphocytes, 7.6 per cent; transitional cells, 2.1 per cent.

Another count on March 17, 1920, was as follows: Red blood cells, 5,608,000 per c.mm.; white blood cells, 8200 per c.mm. Differential white

cell count: neutrophils, 67 per cent; small lymphocytes, 27 per cent; eosinophils, 6 per cent.

Treatment. On March 18, 1920, a pack of radium emanation, consisting of 1852 millicurie hours, with a filter of 2 mm. lead and 0.5 mm. silver, and a radiating area of 70 sq. cm. was applied at 6 cm. focal distance over the spleen for six and a half hours, or a total of 12,038 millicurie hours.

Course. On March 26, 1920, another blood count was obtained: Red blood cells, 6,800,000 per c.mm.; white blood cells, 6,400 per c.mm. Differential white cell count; neutrophils, 91 per cent; small lymphocytes, 9 per cent. On March 27, 1920, the patient complained of cough and dyspnea. She had a well-marked bronchopneumonia involving the right upper, middle and lower lobes. She was slightly cyanotic and died on March 28, 1920. This single heavy irradiation of the spleen was not sufficient to influence the blood count within a period of eight days.

CASE IV.—I. K., a single Jewess, aged fifty-eight years, reported to the Memorial Hospital on September 7, 1917. Her past history was unimportant except for the presence of large varicose veins on her legs for the previous ten years.

Present Illness. In 1911, she noticed conjunctival hemorrhages. An examination by her physician revealed an enlarged spleen. In 1913, she had severe hemorrhages from the rectum and was admitted to another hospital. There her blood pressure was found to be elevated and her red blood count to be high (7,000,000 per c.mm.).

Physical Examination. On admission, she had the appearance of a healthy woman. The spleen and liver were slightly enlarged. There were varicose veins on her legs. Her skin had a peculiar brownish tint and the conjunctival bloodvessels were injected and crimson. Her lungs and heart were normal.

Treatment. Nine months after a cycle of Roentgen irradiation to the spleen and long bones, the following blood count was obtained (July 16, 1918): Red blood cells, 5,920,000 per c.mm.; white blood cells, 7200 per c.mm. Differential white count: Polymorphonuclear leukocytes, 79 per cent; small lymphocytes, 17 per cent; large lymphocytes, 2 per cent; eosinophils, 1 per cent; basophils, 1 per cent.

Course. Her general condition improved and remained favorable until February 1920, when she was lost to further observation.

Summary. 1. Erythremia with splenomegaly can be profitably treated palliatively by irradiation.

2. The treatment should be directed toward the bone marrow rather than the spleen.

3. The hyperplastic bone marrow in this disease is radio-sensitive.

4. The symptoms of plethora are relieved, the general health is improved and life is prolonged by the use of Roentgen rays and radium, but these measures are not capable of preventing the usual fatal termination of the disease.

REFERENCES.

1. Bécélère: Bull. de l'Acad. de méd., 1922, 87, 227.
2. Böttner, A.: Deutsch. med. Wchnschr., 1920, 46, 66.
3. Gutzeit, K.: Münch. med. Wchnschr., 1922, 69, 1569.
4. Hurwitz, S. and Falconer, E. H.: J. Am. Med. Assn., 1918, 70, 1143.
5. Pendergrass, E. P.: Am. J. Med. Sci., 1921, 161, 723.
6. Rydgaard, F.: Hospitaltid., 1921, 64, 379.
7. Schütze, J.: Med. Klin., 1923, 19, 458.
8. Steiger, M.: Schweiz. med. Wchnschr., 1923, 53, 376.
9. Stolkind, E. J.: Lancet, 1923, i, 1312.

THE EFFECT OF AMYL NITRITE ON THE SIZE OF THE HEART AND THE WIDTH OF THE AORTIC SHADOW AS DETERMINED ROENTGENOLOGICALLY.

BY WILLIAM A. BRAMS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE NORTHWESTERN UNIVERSITY MEDICAL SCHOOL;
ATTENDING PHYSICIAN COOK COUNTY HOSPITAL; ASSOCIATE ATTENDING
PHYSICIAN MICHAEL REESE HOSPITAL, CHICAGO,

AND

HERMAN A. STRAUSS, B.S.

(From the Department of Physiology, Northwestern University Medical School and the Frederick K. Babson Fund for Cardiac Research at the Michael Reese Hospital.)

THERE is comparatively little information as to the size of the heart and aorta in man as determined roentgenologically following the use of amyl nitrite. Scherf and Zdansky,¹ with the aid of a special apparatus, found that the transverse diameter of the heart shadow was decreased in 26 of 31 patients so examined during the fall in blood pressure following the use of amyl nitrite. They found that the reduction in width was 10 per cent or less of the original and that the relative proportion during systole and diastole was maintained.

We have conducted a series of experiments to determine if changes occurred in the width of the aortic shadow as well as in the diameter of the heart and if the results depended upon the state of the peripheral vessels or blood pressure. Our material consisted of a series of 21 patients, of whom 6 were normal and in 15 on whom a diagnosis of arteriosclerosis was made clinically on the basis of hard, tortuous radials. Seven of those with arteriosclerosis had a systolic blood pressure far above 160 mm. of mercury. The method of study consisted of placing the patient in the supine position and determining of the blood pressure by the auscultatory method. The patient was then instructed to take a deep breath and to hold it while the control exposure was made. The duration of all exposures was ten seconds in order to obtain the maximum size of the heart during several cycles, in order to exclude the change in size from systole and diastole during a shorter exposure. The cuff of the blood-pressure instrument remained in place for the duration of the experiment, and care was used to keep the patient in the same place on the table while the films were changed. An amyl nitrite pearl was held to the nose of the patient while a wet towel was kept over his face, in order to enhance the effect. Blood-pressure determinations were then made frequently, and a second

exposure, similar to the first, was made as soon as a distinct drop in pressure occurred. The maximum width of the transverse heart diameter and of the aortic shadow were measured in the same interspace as in the control for each patient.

A study of the following table shows that the maximum transverse heart diameter was decreased after amyl nitrite in 18 of the 21 patients studied. This result was constant in the 7 patients with both arteriosclerosis and hypertension. The 5 patients showing neither clinical evidence of arteriosclerosis nor hypertension showed this change in 4 of 5 instances, while the group of 9 patients with clinical evidence of arteriosclerosis, but without hypertension, showed a decreased cardiac diameter in 7 of the 9 cases.

No.	Clinical diagnosis.	Transverse diameter of heart.		Width of aortic shadow.	
		Before amyl nitrite.	After amyl nitrite.	Before amyl nitrite.	After amyl nitrite.
1.	No arteriosclerosis (normal pressure)	14.6	12.6	7.2	7.0
2.	" " "	12.9	11.9	6.3	6.3
3.	" " "	17.0	16.5	8.5	8.6
4.	" " "	14.3	15.0	5.5	6.8
5.	" " "	14.0	13.5	6.0	7.0
1.	Arteriosclerosis (normal pressure)	15.3	14.0	6.4	6.8
2.	" " "	14.2	13.7	7.8	7.9
3.	" " "	10.5	11.3	6.4	7.5
4.	" " "	17.5	15.5	7.0	7.8
5.	" " "	20.0	20.0	7.8	7.5
6.	" " "	13.8	13.0	10.5	10.5
7.	" " "	20.3	19.5	7.5	7.5
8.	" " "	14.0	13.5	6.5	7.5
9.	" " "	14.0	13.2	6.0	6.3
1.	Arteriosclerosis (hypertension)	15.0	14.8	7.5	7.5
2.	" " "	15.5	15.2	7.2	7.0
3.	" " "	21.5	21.0	10.0	11.3
4.	" " "	17.7	15.5	7.0	7.8
5.	" " "	18.8	18.3	7.2	7.5
6.	" " "	19.6	19.0	8.3	8.3
7.	" " "	19.5	18.3	6.0	9.5

The width of the aortic shadow after amyl nitrite was increased in 13 of the 21 patients. The frequency of this change was about the same in all groups.

The changes in the transverse diameter of the heart coincide closely with those found by Scherf and Zdansky, both in frequency of occurrence and in degree. The maximum reduction was 2.2 cm., and the average was a little under 10 per cent of the diameter prior to the administration of the amyl nitrite. The increased width of the aortic shadow was also of similar degree.

The reduction in size of the heart following the administration of amyl nitrite may be due to two factors: The increased rapidity

of the heart rate would cause a more frequent emptying and a shorter diastolic period resulting in less blood entering the heart during diastole. The dilatation of the vessels by amyl nitrite would induce a displacement of more blood toward the vessels and away from the heart, thus further reducing the quantity of blood contained in the heart during diastole.

The increased width in the aortic shadow is more difficult to explain. Part of this increase may be due to dilatation of the aorta, but the other great vessels included in this shadow must also be considered. The effect of amyl nitrite, according to Sollmann,² is directly on the vessel wall, resulting in dilatation, particularly of the arterioles in the splanchnic region. The veins also become engorged, but the displacement of large quantities of blood to the arterioles of the splanchnic area results in a fall of pressure in the venous system. It is conceivable, therefore, that the vessels included in the aortic shadow, but which carry venous blood, may play a prominent part in the increased width of the shadow. The presence of arteriosclerosis seemed to have no effect in limiting the change in width of the shadow, but there is no way of telling if sclerosis of the aorta was present or absent in spite of its presence in the radial arteries.

Summary. 1. The size of the cardiac and the aortic shadow was studied roentgenologically in a series of 21 patients before and after administration of amyl nitrite.

2. The group studied included 6 normal persons and 15 showing clinical evidence of arteriosclerosis, with and without hypertension.

3. The transverse diameter of the heart shadow was reduced after amyl nitrite in 18 of the 21 persons studied. The presence or absence of arteriosclerosis or hypertension seemed to play a minor rôle in these changes in diameter.

4. The width of the aortic shadow was increased in 13 of the 21 patients after amyl nitrite. This result also seemed to be independent of the condition of the peripheral vessels or degree of blood pressure.

5. The changes in the cardiac diameter may perhaps be explained by the decreased content in the heart during diastole because of the rapid rate and displacement of blood into the dilated blood-vessels and away from the heart.

NOTE.—We wish to acknowledge the technical help given by the Roentgenologic Department of the Michael Reese Hospital.

REFERENCES.

1. Scherf, D., and Zdansky, E.: *Wien. Arch. f. inn. Med.*, 1929, 16, 399.
2. Sollmann, T.: *A Manual of Pharmacology*, 1926, p. 492.

STREPTOCOCCUS VIRIDANS ENDOCARDITIS IN CHILDREN.

REPORT OF FIFTEEN CASES AND OF ONE INSTANCE OF STREPTOCOCCUS VIRIDANS SEPTICEMIA WITHOUT ENDOCARDITIS.

BY CLIFTON B. LEECH, M.D.,

PHYSICIAN IN CHARGE, CARDIAC CLINIC, HARRIET LANE HOME FOR INVALID CHILDREN.

(From the Department of Pediatrics, Johns Hopkins University School of Medicine and the Harriet Lane Home, Johns Hopkins Hospital.)

STREPTOCOCCUS viridans endocarditis is comparatively uncommon in children. Among 317 cases cited by Blumer,¹ but 1 occurred under the age of ten years. The incidence of subacute bacterial endocarditis in children under ten years of age at the Massachusetts General Hospital was 1.7 per cent, according to Lawson and Palmer,² who reported a case of Streptococcus viridans septicemia without demonstrable valve lesions in a child aged twenty-one months. Schlesinger³ cited an instance, not proven by culture, in a child under five years. In a recent review of the literature Rost and Fischer⁴ found no proven case under five years of age; it occurred most frequently from the age of seven to twelve years. These authors report 10 new proven cases, 1 probable example with no growth in the blood culture and 1 Bacillus influenzae endocarditis. They describe the general symptomatology in children, including the pigmentation of the skin (*café au lait*) which has been emphasized by Libman as characteristic of subacute bacterial endocarditis. Rost and Fischer call attention to the wide variation in the duration of the disease, but give no figures concerning their own cases in this respect. Each of their patients had petechiæ; only 1 failed to evidence some additional sort of embolic phenomena, while only 2 failed to show hematuria. In 9 of their patients the Streptococcus viridans infection was secondary to chronic rheumatic heart disease and one had a history of rheumatism. Congenital heart disease was present in 1 of their patients and was noted in 5 of the 64 cases which they reviewed.

The classical studies by Thayer⁵ based upon 67 instances of proven Streptococcus viridans endocarditis offer an accurate picture of the general nature of this disease. Exact ages are not recorded, but the incidence is given as 5.6 per cent in the first decade and as 8.4 per cent in the second. The duration in more than one-half of the cases was beyond five months, while in only 4 patients did death occur within six weeks from the onset. There was one apparent recovery. More than 80 per cent of the infections were secondary to chronic valvular disease, almost always rheumatic in nature, but in rare instances of syphilitic origin. The instances in which the

Streptococcus viridans was the sole invader were chiefly those of rapidly fatal outcome. At one necropsy acute rheumatic myocarditis was found to accompany acute viridans endocarditis. The portal of infection was difficult to determine, but in about one-third of the patients the malignant endocarditis seemed to follow rather closely an acute infection, such as respiratory infections, tonsillitis or sinusitis, puerperal infections, mumps, smallpox, appendicitis, gonorrhea and others. About one-half of the victims had pyorrhea alveolaris or periapical abscesses. One or two general viridans infections followed closely upon extraction of teeth. Fever was intermittent in about 80 per cent of the patients, was constant in the remainder and one-third of the total had chills. The spleen was palpable in about one-half the cases, especially in the late stages of the disease. In about 66 per cent of the viridans infections there occurred various embolic phenomena, such as small, nodular, erythematous, painful, cutaneous swellings in the extremities; petechiæ with white centers (described by Libman); tenderness in the splenic region; showers of red corpuscles in the urinary sediment without evidences of grave nephritis; paralyses and acute psychic disturbances. Nearly every patient showed albuminuria, but in less than 50 per cent did acute or subacute nephritis occur. Anemia was common, and there was great variation in the leukocyte count, a leukocytosis constituting the rule. Pericarditis was an infrequent complication. The mitral valve was involved in 85 per cent, the aortic in 50 per cent, the tricuspid in 15 per cent and the pulmonary in 5 per cent of these autopsied infections. A small percentage had congenital defects of the heart, although 43 per cent showed Hippocratic fingers. The findings revealed by Thayer's analysis, derived chiefly from adult case records, are fairly applicable to *Streptococcus viridans* endocarditis in children, the most striking differences occurring in the much smaller percentage of true nephritis and Hippocratic fingers in the children.

The following summary is typical of the history and course of *Streptococcus viridans* endocarditis superimposed upon a chronic rheumatic endocarditis in a child:

CASE I.—R. D. No. 20882. At the age of ten years a white girl, whose previous history included measles and joint pains, developed scarlet fever from which she recovered with no sequelæ except development of a diastolic cardiac murmur suggestive of aortic insufficiency. At the age of twelve years a mild rheumatic fever was accompanied and followed by development of the signs of mitral stenosis and mitral insufficiency. At thirteen her tonsils and adenoids were removed. A few months later she was admitted to the Harriet Lane Home with a moderately severe acute rheumatic fever; during the convalescence there appeared a painful red, rough, blotchy swelling along the lateral surface of the left forearm. This indurated swelling included many dilated bloodvessels and a few small intradermal hemorrhages. There was no growth in the blood culture at this time and the diagnosis of erythema nodosum hemorrhagica was made. The rheumatic fever recurred from which she slowly recovered to be discharged to a con-

valescent home. She remained comparatively well for fourteen months when she awoke one morning with paresis of the left face, arm and leg, which gradually improved. About this time fever and pain in various joints appeared by reason of which she was readmitted to the Harriet Lane Home, where the essentials of the physical examination were found to be prostration, pallor, widespread petechiæ, left-sided paresis, characteristic signs of cardiac enlargement with aortic insufficiency, mitral insufficiency and mitral stenosis, left ankle clonus and a positive Babinski, and a large, pink, swollen, tender area on the dorsum of the foot. The leukocyte count was 19,000, hemoglobin 52 per cent; there was a trace of albumin in the urine and a growth of *Streptococcus viridans* in the blood culture. In the course of a few days the tips of the left index and middle fingers became red and painful. Small furuncles developed in these areas and within a week the inner surfaces of all the fingers of the left hand were distinctly bluish and suggestive of gangrene. During this time petechiæ appeared in various areas, including the palpebral conjunctivæ, and pain was complained of in various joints. The temperature remained between 38.3° and 39.4° C. There was gradual loss of strength but the child remained conscious until the day of death about one month after the final admission to the hospital. At no time were the spleen and liver palpable or tender. There was no hematuria. The autopsy revealed a *Streptococcus viridans* endocarditis of the mitral and aortic valves secondary to a chronic endocarditis in the same areas. There was a mural thrombus; cardiac hypertrophy and dilatation; old and fresh infarcts of the spleen, kidney and brain; chronic passive congestion of the lungs, liver and spleen; acute nephritis, and petechial hemorrhages over the pleural and peritoneal surfaces. (It is not unusual for autopsy to reveal nephritis and infarcts of the spleen and kidney, no evidence of which appeared clinically.)

The following summary is typical of the history and course of a primary *Streptococcus viridans* endocarditis:

CASE II.—G. S. No. 62782. A white girl aged twelve years, had influenza in December, 1928, and never was strong thereafter. The only previous illnesses were numerous sore throats, with a tonsillectomy at the age of five years, and measles at the age of seven. After convalescence from the influenza her attendance at school was irregular because of her easy fatigability. She had some fever every day, her lips were swollen at times and red spots occasionally appeared over the face. In February she became so weak and complained so much of pains in her joints that she was sent to a hospital where improvement occurred but from which she was removed against advice after eight weeks. Soon after returning home she complained of severe pains in the left shoulder and the left upper quadrant of her abdomen; there also was a constant ache under her left knee in the region of the hamstring tendons. A week later there was twitching of the left side of the face and involuntary movements of the left hand. She was then admitted to the Harriet Lane Home where the important features revealed by physical examination were fever, tachycardia, emaciation, hemoglobin 55 per cent, erythrocytes 4,000,000, one carious tooth, coarse râles in the bases of the lungs, cardiac enlargement with a systolic murmur heard best at the apex and not widely transmitted, distinctly palpable, nontender spleen and liver, several pinkish blotches scattered over the extremities, paresis of the left facial and brachial muscles, and a poorly sustained left ankle clonus.

During her stay in the hospital a few petechiæ appeared, including one in the ocular conjunctiva. The paralysis gradually disappeared and no further signs of embolism developed. She became entirely free from pain. Fever occurred only in the evening. Repeated blood cultures showed from

seventy to two hundred colonies of *Streptococcus viridans* per cubic centimeter of blood. Similar organisms were cultivated from the throat. The heart signs and size of the spleen remained unchanged. At the end of five weeks the patient was up and about the ward and was permitted to return home.

Throughout the summer petechiæ appeared infrequently; there was occasional swelling of the ankles and one attack of pain in the left hypochondrium. During a two-day period in October dizziness and vomiting occurred, after which she complained of photophobia and diplopia. Her appetite became poor and she was admitted to the Harriet Lane Home for the second time on October 28, 1929. Examination revealed prostration, anemia, fever, cardiac enlargement with a loud blowing systolic murmur heard over the entire chest and well into the axilla, palpable spleen (larger than at the previous admission), moderate enlargement of the liver, bilateral unsustained ankle clonus, and nystagmus. She rapidly became weaker, was unable to take fluids, developed a tachycardia of 160, and died November 2, 1929, without the appearance of further petechiæ. The autopsy revealed bacterial endocarditis of the mitral valve only, acute splenic tumor with infarcts, chronic passive congestion of the liver, hydropericardium, acute nephritis, and hyperplasia of bone marrow.

The records of the Harriet Lane Home reveal 13 instances of *Streptococcus viridans* endocarditis, proven by blood culture or by autopsy, 2 unproven but highly probable cases and 1 *Streptococcus viridans* septicemia without endocarditis. The 15 cases represent an incidence of approximately 0.1 per cent. Analysis of these records is partially indicated in the accompanying table and is more fully discussed below.

AGE. Although the earliest definite age at which *Streptococcus viridans* has been reported is five years, it occurs in this series in one autopsied patient, aged four years and three months, in an undoubted instance at the age of four years and five months and in another at the age of three years and seven months. A *Streptococcus viridans* septicemia without endocarditis was revealed in the autopsy of an infant aged fifteen and a half months. Fifty per cent of the children with this disease were under ten years of age, but it is apparently very uncommon under the age of five years.

PORTAL OF ENTRY. The portal of entry cannot be determined with certainty in any instance, but the onset closely followed extraction of teeth in 2 of these patients; it accompanied and followed influenza complicated by a *Streptococcus viridans* infection of the throat in a third, and closely followed an acute tonsillitis in 1 patient, pertussis in another patient and had its apparent beginning three weeks after vaccination in another. Three children were recorded as having markedly carious teeth. From a child, admitted to the hospital a second time for acute rheumatic fever and chorea, *Streptococcus viridans* was found in the blood culture, but there were no evidences of endocarditis or septicemia, except the signs of chronic rheumatic lesions, until late in the duration of the infection when a right hemiplegia, Osler's nodes and severe abdominal pain made their appearance.

Age.	Duration.	Primary heart lesion.	Petechiæ.	Palpable spleen.	Paralyses.	Hemo- globin, per cent.	Red cell count, millions.	Leucocyte count.	Blood culture.	Autopsy.
12 yrs. . .	11 mos.	Strep. viridans	Widespread	Yes	Left facial and brachial	55	4.00	9,000	70-200 colonies Strep. viridans	Yes
10 yrs. . .	1 mo.	Rheumatic heart disease	Widespread	No	Left-sided, complete	52	19,000	Strep. viridans	Yes
4 yrs., 3 mos.	2 mos.	Congenital malforma- tion—pulmonary sten- osis, patent interven- tricular septum	None	Yes	No	50	3.00	12,000-30,000	Strep. viridans	Yes
10 yrs. . .	10 wks.	Rheumatic heart disease	None	No	Slight, right	35-65	3 to 4	6,000-9,000	Strep. viridans, 15-150 colonies per cc.	Yes
7 yrs. . .	3 mos.	Rheumatic heart disease	Eyelids	Yes, 2 em.	No	55	10,000	Strep. viridans	No
4 yrs., 5 mos.	1 mo.	Rheumatic heart disease	None	No	No	80	17,600	Postmortem.	No
8 yrs., 5 mos.	6 to 8 wks.	Probable rheumatic heart disease	None	Yes	No	12,900	Strep. viridans	No
13 yrs. . .	10 mos.	Rheumatic heart disease	Conjunctivæ, fingers, torso	2 em., tender	No; convul- sions	58	4.70	22,000	Strep. viridans, 150 colonies per cc.	No
3 yrs., 7 mos.	1 mo.	Probably Strep. viridans	Torso	No	No	60	4.40	12,700	Strep. viridans	No
14 yrs. . .	2 mos.	Congenital heart disease —probably patent sep- tum	Right thigh	No	No	3.20	4,000	Strep. viridans	No
8 yrs. . .	3 mos.	Probable congenital heart disease	None	No	No	60	4.85	16,000	Strep. viridans	No
11½ yrs. . .	8 mos.	Rheumatic heart disease	Conjunctivæ, abdomen, finger tips	2 to 3 em.	No	65	5,650	Strep. viridans	No
9½ yrs. . .	3 mos.	Probably Strep. viridans	Conjunctivæ, extremities	Yes, tender, 1 to 2 em.	No	33	14,600	No growth	No
11 yrs. . .	3 mos.	Rheumatic heart disease	Conjunctivæ	1 em.	No	45	3.90	20,500	Strep. viridans	No
6 yrs. . .	1 wk.	Probably Strep. viridans	Widespread: lit- tle finger, right, gangrenous be- tween 1st and 2d toes, right; redness and swelling of 3d finger, left	2 em.	Left arm	Un- known	Unknown	Contaminated	No
15½ mos.	2 wks.	No heart lesion	Gangrene be- tween 1st and 2d toes, right; redness and swelling of 3d finger, left	No	No	65	43,000	Postmortem, Strep. viridans	Yes*

* Strep. septicemia without endocarditis.

PRIMARY AND SECONDARY INFECTION. In 1 case it was proven by autopsy that the viridans organism was a primary invader. In 3 other instances, not proven by autopsy, the evidence pointed toward the primary viridans endocarditis. In 1 autopsied patient the viridans endocarditis was superimposed upon a congenital malformation (pulmonary stenosis and patent interventricular septum), while in 2 others the same thing apparently occurred, but necropsy was not done. In 8 instances there is clear evidence of a rheumatic heart lesion preceding the infection by the *Streptococcus viridans*.

DURATION. Every patient succumbed. The duration, as nearly as can be estimated from the onset of symptoms and signs, varied from one week to eleven months, with about one-half the victims living for two or three months after the onset. The duration in the instances of primary invasion was not strikingly different from that of those in which the organism was a secondary invader; the shortest (one week) and the longest (eleven months) occurred in the primary group.

MANNER OF ONSET. The appearance of symptoms for the most part was gradual, with lassitude, weakness and pallor prominent features. In 3 children the onset was distinctly abrupt and accompanied by chills, while in a fourth chills occurred at a later stage of the infection. As may be judged by the duration, there was usually a progressively downward course, but improvement did occur temporarily in 3 patients. There was no distinct remission with freedom from all signs and symptoms.

FEVER. The fever was characterized by its irregularity and wide range. One patient ranged in twenty-four hours from 37.5° to 42.1° C. and back to 39.4° C. Another patient had a fever of 42.5° C. the day of death. In about one-half of the children the fever was intermittent, the temperature at times falling to normal or below. In about 50 per cent of the temperature charts the curve for the most part ran between 37° and 38° or 38.5° C., with occasional drops to subnormal, while the remainder ranged in the higher temperatures from 38.2° to 40° C., with occasional drops. As a rule, there was a morning drop and an evening rise in the fever of 2° C. or more. The striking feature was the marked irregularity of the curve. In more than one-half of the patients the fever was intermittent as well as irregular.

PETECHIÆ, NODES, HIPPOCRATIC FINGERS AND SPLENIC ENLARGEMENT. In one-third of the children petechiæ were not seen at any time, in another third they were infrequent and inconstant, but were widespread in the remainder. The conjunctivæ were a common location for these. Osler's nodes were described in 3 patients only. Clubbing of the fingers occurred in 3 patients, in 2 of whom congenital heart lesions probably existed. The spleen was definitely palpable in 9 of the children and was distinctly tender in 2. The liver was apparently enlarged in 7 instances.

PARALYSES AND GANGRENE. Four patients showed partial or complete paresis of the right or left extremities. Two children had gangrene of the fingers and toes, and another presented convulsions which were thought to be due to cerebral emboli.

HEMATURIA AND URINARY FINDINGS. In none of the patients was obvious hematuria recorded, while the urinary findings for the most part were not remarkable. In 5 instances the findings were entirely normal, in 4 the sole abnormality consisted of the presence of albumin, while in 3 there were casts as well as albumin. Red blood cells were seen in the sediment in 4 cases only.

PIGMENTATION, ANEMIA AND LEUKOCYTOSIS. In 1 patient the distinctive *café au lait* color of the skin was described while 2 were recorded as having a lemon-yellow tint and 3 others presented a marked pallor. In the remainder no mention was made of pigmentation or pallor. Anemia with respect to hemoglobin was a striking feature of the clinical picture, but the red count did not seem to be proportionately diminished. Hemoglobin values varied from 33 to 65 per cent as a rule. The red cell count varied from 3,000,000 to 4,850,000. The leukocyte count was increased in most of the children, only 4 having a normal or low count. There was no strikingly apparent association between virulence of the infection, as shown by its duration, and the height of the leukocytosis, but it is noticeable that the patients with normal or subnormal leukocyte counts had a longer duration than average.

HEART SIGNS. The patients with congenital heart disease presented no heart signs which of themselves permitted differentiation between the acquired and the congenital lesions. This is also true of instances of viridans endocarditis superimposed upon chronic rheumatic valvular disease. In these instances there usually occurred, however, sufficient change in the character of the sounds and murmurs to indicate some sort of change in the heart. In nearly every patient there was a widely transmitted systolic murmur heard best in the apical region. Frequently this murmur became considerably intensified late in the disease. In one-third of the children a precordial systolic thrill, usually apical, appeared sooner or later in the course of the infection. Enlargement of the heart was usually present but was not marked.

LOCATION OF ENDOCARDIAL INFECTION. In no instance was there evidence to indicate infection of the pericardium by the *Streptococcus viridans*. In the cases which came to autopsy the mitral valve was solely involved in one instance, was affected in combination with the aortic valve in another patient, in combination with the tricuspid in a third, while in the fourth the seat of the viridans infection was the congenitally deformed pulmonary valve. In those which did not come to autopsy it was thought probable in every instance that the mitral valve was involved, and in 3 patients it was considered likely that the aortic valve was also the seat of

the infection. In none of the children was a diagnosis of tricuspid or pulmonary endocarditis suggested.

Summary. There is offered a brief discussion of descriptions which appear in the literature of *Streptococcus viridans* endocarditis along with an analysis of 15 previously unreported cases in children proven by blood culture or autopsy. Three of these occurred under the age of five years. Mention is made of a *Streptococcus viridans* septicemia without endocarditis occurring in an infant of fifteen and a half months.

It is evident that this infection produces a clear-cut clinical picture with sufficiently constant characteristics to permit diagnosis even without culture of the blood. The onset is usually gradual, with lassitude, weakness and pallor the common features, but occasionally with chills and abrupt appearance of fever and prostration. About 75 per cent of these infections are superimposed upon rheumatic valvular lesions or congenital defects of the heart. The course is progressively downward, with a duration of one month to one year, ordinarily two or three months only. The fever is intermittent and widely irregular. Two-thirds of the patients have petechiæ and palpable spleens, which are sometimes tender. The liver is enlarged in about one-half of the instances. Osler's nodes occur occasionally and clubbing of the fingers is an infrequent accompaniment. Paresis occur in about 25 per cent of the victims, while gangrene of the fingers or toes is an occasional incident. The urinary findings vary from normal to obvious hematuria and evidences of acute nephritis. Pallor, sometimes described as having a yellowish or *café au lait* tint, may be expected, especially in the late stages. Marked diminution of the hemoglobin content is almost invariable, but with a slight or moderate diminution in the number of red cells. A leukocytosis is the rule. The heart signs are dependent upon the location of the endocardial infection which is most often at the mitral valve, resulting in a blowing systolic murmur best heard at the apex and accompanied in one-third of the patients by a systolic precordial thrill. Slight to moderate cardiac enlargement is ordinarily present.

REFERENCES.

1. Blumer, G.: Subacute Bacterial Endocarditis, *Medicine*, 1923, 2, 105.
2. Lawson, G. M., and Palmer, Robert S.: The Occurrence of Subacute Bacterial Endocarditis in Childhood, *New England J. Med.*, 1928, 199, 1205.
3. Schlesinger, B.: Subacute Infective Endocarditis in Childhood, *Brit. J. Child. Dis.*, London, 1928, 25, 33.
4. Rost, W. L., and Fischer, A. E.: Subacute Bacterial Endocarditis in Childhood, *Am. J. Dis. Child.*, 1928, 36, 1144.
5. Thayer, W. S.: Bacterial (Infective) Endocarditis, *Johns Hopkins Hosp. Rep.*, 1926, 26, 1.

AURICULAR FIBRILLATION AND FLUTTER IN METASTATIC GROWTHS OF THE RIGHT AURICLE.

BY ARTHUR M. FISHBERG, M.D.,

ASSOCIATE PHYSICIAN, BETH ISRAEL HOSPITAL; ADJUNCT PHYSICIAN
MOUNT SINAI HOSPITAL, NEW YORK CITY.

(From the Medical Services of the Mount Sinai and Montefiore Hospitals, New York City.)

IN the large majority of instances, neither benign nor metastatic malignant tumors of the heart produce symptoms. Exceptionally, however, such growths do form the anatomic basis of striking clinical manifestations, which is of course almost always true of the primary malignant neoplasms of the heart. Nevertheless, even in the instances in which they have produced outstanding symptoms, none of these varieties of tumor of the heart has been recognized unequivocally prior to necropsy. Reviewing the casuistic surveys of tumors of the heart published by Pic and Bret,¹ Huchard,² Link,³ and Perlstein,⁴ it seems clear that the difficulty in diagnosis results from the fact that the variegated clinical pictures presented by tumors of the heart simulate much more common diseases, which are naturally diagnosed by the clinician. Among the clinical pictures behind which tumors of the heart have been observed to masquerade are the following:

1. Mediastinal tumor, with symptoms of compression of various mediastinal structures.
2. The banal manifestations of a failing heart, the cause of the myocardial insufficiency remaining obscure during life.
3. Sudden death, which may or may not be preceded by symptoms of cardiac disease.
4. Mitral stenosis, with symptoms of myocardial insufficiency, presystolic murmur, and accentuated pulmonic second sound; these cases are due to a pedunculated myoxma or myxofibroma* of the left auricle which protrudes through the mitral valve into the left ventricle (Thompson and Aclison,⁹ 2 cases). In the remarkable instances of this type reported by Virchow¹⁰ and Robin,¹¹ the predominant symptoms were the result of emboli arising from thrombi on the surface of the tumor.
5. Tricuspid stenosis with a presystolic murmur in the tricuspid area for ten years, shown at necropsy to be due to a pedunculated

* Doubt has been expressed that these pedunculated structures are true myxomas or myxofibromas; some hold them to be merely organized thrombi, as was true in a case reported by Oppenheimer and Ehrenreich.⁵ But recent authorities (Kaufmann,⁶ Ribbert,⁷ Ewing⁸) agree that the majority are true blastomas.

fibroma of the right auricle protruding through the tricuspid valve (Gairdner¹²).

6. Aortic insufficiency, with symptoms of cardiac failure, an aortic diastolic murmur and enlargement of the heart, due to a primary tumor of the aortic cusps (Prudhomme¹³).

7. Recurrent hemorrhagic pericardial effusion; in Fraenkel's¹⁴ case of primary sarcoma of the right auricle four aspirations were required, while in the sarcoma of the left auricle observed by Beck and Thatcher¹⁵ the roentgenogram was that of pericardial effusion. In the subepicardial sarcoma studied by Perlstein,⁴ there was recurring bloody pleural effusion.

8. Angina pectoris, due to multiple growths, probably sarcomatous, of the right ventricle (Ingram¹⁶).

9. Heart block with Stokes-Adams syndrome due to a lymphangioendothelioma arising in the auriculoventricular node (Armstrong and Moenckeberg¹⁷).

10. Rhabdomyomas are associated in more than 50 per cent of cases (Wolbach)¹⁸ with tuberous sclerosis of the brain, the symptoms of which constitute the clinical picture.

In the present communication, I desire to report 3 cases in which secondary malignant growths in the wall of the right auricle were accompanied by auricular fibrillation or flutter. In each of the 3 cases the appearance of the arrhythmia led during the life of the patient to the opinion, with increasing conviction in the successive cases, that the known malignant disease had invaded the right auricle.

Case Reports. CASE I.—J. L., a male aged sixty-nine years, was admitted to Mount Sinai Hospital August 19, 1926, complaining of pain in the right chest. His illness dated back about three months, during which time he lost about 37 pounds in weight, became progressively weaker, and suffered from severe pain throughout the right chest. Shortly before admission, he developed dyspnea, orthopnea and nocturia.

On admission, physical signs of copious effusion into the right pleura were found and 1900 cc. of bloody fluid were aspirated. Radiography after aspiration disclosed a large mass in the region of the hilus of the right lung which was considered to be a bronchial carcinoma. This diagnosis was confirmed by bronchoscopy which revealed a fungating mass at the beginning of the right main bronchus. A specimen was removed which proved to be carcinoma on histologic examination.

During the first twelve days of the patient's stay in the hospital, the rhythm of the heart was regular, although the rate was moderately accelerated. An electrocardiogram taken on the day of admission showed only inversion of the T wave in the third lead. September 1, auricular fibrillation was discovered, which persisted until the patient's death on September 4. The clinical picture in the last days was dominated by intense orthopnea, the patient sitting with feet hanging over the side of the bed, head flexed on the trunk, spine in lordosis, and hands folded across the chest. Toward the end, the cyanosis became intense.

Bearing in mind the location of the tumor at the right hilus, the onset

of auricular fibrillation led to the suspicion that the growth had invaded the right auricle.

At necropsy, there was found a huge, breaking-down tumor of the right main bronchus infiltrating the entire right lower lobe and extending into the right anterior chest wall, the right dome of the diaphragm and the mediastinum.

Examination of the heart revealed that the growth had infiltrated the posterior surface of the right and left auricles down to the endocardium; in fact, the tumor had broken through the endocardium of the left auricle for an area of about 3 mm. in diameter. The involvement of the posterior wall of the auricles extended down to the auriculoventricular junction and up along the superior vena cava and pulmonary artery, especially the left branch.

CASE II.—A. R., male, aged sixty-four years, was admitted to Montefiore Hospital December 6, 1927. In March, 1927, he began to cough, feel weak and lose weight. All these symptoms gradually became aggravated. For two months before admission he also suffered from dyspnea and orthopnea.

Physical and radiographic examination revealed evidences of a tumor in the right upper lobe. This diagnosis was confirmed by bronchoscopy, which disclosed a large ulcerating mass obstructing the right bronchus.

On December 9, auricular fibrillation appeared. This arrhythmia persisted until December 11, when the heart again became regular. On December 15, auricular fibrillation was again detected and persisted until the death of the patient with the picture of circulatory failure on December 22. The outstanding symptoms in the last days were agonizing orthopnea and intense cyanosis.

When auricular fibrillation set in, a diagnosis of carcinomatous involvement of the right auricle was made by Dr. Julius Gottesman (to whose kindness I owe the opportunity of seeing this case), on the basis of the findings in Case I.

At necropsy, a large carcinoma arising from the right main bronchus was found. The bronchial glands were enormously enlarged by carcinomatous infiltration. The growth had invaded the posterior wall of the right auricle, infiltrating it extensively down to the endocardium. There was no involvement of any other part of the heart by carcinoma. There was moderate coronary arteriosclerosis without any actual occlusion, and slight atheroma of the mitral and aortic valves.

CASE III.—S. B., a male, aged sixty-five years, was admitted to Mount Sinai Hospital, December 2, 1929. He had first noted painless swellings on both sides of his neck about three months before admission. These had gradually increased in size up to the time he entered the hospital. For some time he had had occasional pain in the left anterior chest which radiated to both shoulders; it had no relation to exertion but was occasionally associated with dyspnea.

On admission, there were numerous greatly enlarged lymph glands in the neck, extending from the clavicle to behind the ears. The inguinal and epitrochlear glands were also enlarged, but the spleen was not palpable. One of the cervical glands was removed and histologic examination revealed reticulum-cell sarcoma. Under radiotherapy, the glands rapidly diminished in size and the patient was discharged for ambulant treatment January 5, 1930.

On January 8, 1930, he was readmitted. He stated that on the way home from the hospital he had been seized by a severe constricting pain

extending from the suprasternal notch to the xiphoid process; the pain radiated to the left shoulder and down the ulnar side of the left arm to the tip of the little finger. He became faint and suffered from dyspnea, palpitation and cough. Later, the cough was accompanied by a choking sensation. Despite several hypodermic injections, these symptoms persisted and he was brought back to the hospital on January 8.

The patient was intensely orthopneic and sweated profusely. He also suffered from anginal pain almost continuously; the attacks followed one another at such short intervals as to warrant their description as status anginosus. The attacks were of the type described above and so severe that they were controlled to but a slight degree by large doses of morphin. There was cutaneous hyperesthesia in the precordial region. Presystolic gallop rhythm appeared. The blood pressure, previously 160 mm. systolic and 80 mm. diastolic, fell to 96 mm. systolic and 82 mm. diastolic.

On January 9, the electrocardiogram revealed the presence of auricular flutter with 2 to 1 auriculoventricular ratio. The ventricular rate was 150 per minute. An electrocardiogram the next day showed that the flutter was still present. However, on January 12, normal sinus rhythm returned and remained until death, which occurred on January 24.

When auricular flutter appeared, that is, fifteen days before death, it was thought probable that the neoplasm had involved the right auricle.

At necropsy, widespread enlargement of the lymph nodes due to reticulum cell sarcoma was found. There was also extensive infiltration of the spleen, liver, kidneys and bone-marrow.

The heart: The pericardium was adherent to the pleura. The heart weighed 350 gm. The heart chambers were negative. The posterior and lateral walls of the right auricle were thickened by infiltration with grayish-white tumor tissue. The infiltration extended to the endocardium but did not perforate the latter. It reached from the entrance of the superior vena cava almost to that of the inferior vena cava. In the wall of the left ventricle were two infiltrations of tumor tissue; one was situated not far from the apex, while the other, a mass about 2 cm. in diameter, completely surrounded the circumflex branch of the left coronary artery, resulting in marked narrowing of the lumen. One papillary muscle in the left ventricle was infiltrated by tumor tissue. The right ventricle and left auricle were negative. The mitral and tricuspid valves were slightly thickened and colored yellow. The descending branch of the left coronary artery showed atheromatous thickening on one side throughout its course but was nowhere occluded.

Comment. Three cases are presented in which auricular fibrillation or flutter appeared in individuals suffering from malignant neoplasms. In the first of the cases, the possibility was considered, when the fibrillation appeared, that the growth had implicated the right auricle; in the 2 later cases, this diagnosis was considered highly probable. At necropsy, the diagnosis of secondary neoplasm of the right auricle was verified in each of the cases; in 1, the right auricle was the only chamber involved, in the other 2, there was also implication of other parts of the heart.

Of course, auricular fibrillation or flutter may occur in individuals with malignant neoplasms from causes entirely independent of the tumor, such as coronary artery disease with consequent myomalacia, old rheumatic valvular and myocardial disease, and others. And

it is conceivable that occasionally in cases in which breaking-down neoplasms lead to such toxic symptoms as fever, auricular fibrillation may also be a manifestation of the "toxemia," much as it not uncommonly occurs in acute febrile infections. But in our cases there was no evidence that any of these causes was operative in inciting the fibrillation or flutter, for which reason we surmised during the life of the patients that the malignant disease had involved the right auricle. It is true that in two of the patients well marked coronary arteriosclerosis was found, but in neither case was there actual occlusion or even great narrowing, let alone myomalacia or scarring consequent on the arterial disease. It would therefore seem improbable that the coronary sclerosis played any part in the genesis of the arrhythmias.

Auricular fibrillation or flutter apparently does not occur in every instance in which malignant disease implicates the right auricle. I have seen several cases in which secondary malignant growths of the right auricle were found at necropsy and no arrhythmia of the pulse was noted clinically. In most of these, it is true, as little attention was devoted to the accurate study of the cardiovascular system as is usually accorded in patients suffering from advanced malignant disease. In one case, however, in which necropsy revealed extensive sarcomatous infiltration of the walls of all four chambers of the heart, pulsus bigeminus was observed and proved by the electrocardiogram to be due to alternate premature beats of the auricle. I am at a loss to explain why neoplastic disease of the right auricle produces in some instances auricular fibrillation or flutter, while in others the rhythm of the heart is unaffected, and in still another neoplastic involvement of both auricle resulted in only auricular premature beats. This inability to explain the presence or absence of the arrhythmia is, however, scarcely surprising, for study of the literature (see the detailed survey by Moenckeberg¹⁹) reveals that there is no definite knowledge of the anatomic basis of auricular fibrillation or flutter in any of the diseases in which these arrhythmias occur. In our cases, the malignant infiltration of the posterior wall of the right auricle was so extensive that there can be no doubt that the specialized tissue comprising the sino-auricular node was at least severely injured and probably largely destroyed.

The pathogenesis of the violent anginal pains in the last sixteen days of life in Case III remains unclear. The precordial pain—constricting in character, radiating to the left shoulder and down the inner side of the left arm to the little finger, and accompanied by precordial cutaneous hyperesthesia—was the classical picture of angina pectoris. The extreme violence of the pain, the accompanying ashy cyanosis and drop in blood pressure led some members of the staff to a confident diagnosis of coronary thrombosis. But

because of the fact that the patient had not had anginal pains previous to the last weeks of life when his activities were greatly restricted, others thought it probable that the anginal pains were manifestations of the malignant disease. At necropsy, no coronary thrombosis was found and the degree of coronary arteriosclerosis seemed insufficient to account for the status anginosus with extreme myocardial insufficiency that had been present. It is tempting to believe that the marked constriction of the circumflex branch of the left coronary artery by a tumor mass was the cause of the status anginosus, but this cannot be considered as by any means established. Another possibility is that the anginal pain resulted from implication of the cardiac nerves in the large sarcomatous mediastinal lymph nodes.

Summary. Three cases are described in which secondary malignant growths in the right auricle were accompanied by auricular fibrillation or flutter. In the first of these cases, the involvement of the right auricle by the tumor was suspected during life, in the two succeeding cases this diagnosis was considered very probable.

REFERENCES.

1. Pic and Bret: *Cancer secondaire du cœur*, *Rev. de méd.*, 1891, 11, 1022.
2. Huehard: *Traité clinique des maladies du cœur*, 3d ed., Paris, 1903, 3, 871.
3. Link: *Die Klinik der primaeren Neubildungen des Herzens*, *Ztschr. f. klin. Med.*, 1909, 67, 272.
4. Perlstein: *Primary Sarcoma of the Heart*, *AM. J. MED. SCI.*, 1918, 156, 214.
5. Oppenheimer and Ehrenreich: *A Pedunculated Cardiac Polyp*, *Proc. New York Path. Soc.*, 1912, 12, 217.
6. Kauffmann: *Lehrbuech der speziellen pathologischen Anatomie*, 7th ed., Berlin, 1922, 1, 63.
7. Ribbert: in Henke and Lubarsch's *Handbuech der speziellen pathologischen Anatomie*, Berlin, 1924, 2, 277.
8. Ewing: *Neoplastic Diseases*, 3d ed., Philadelphia, 1928, p. 189.
9. Thompson and Atchison: *Two Cases of Tumor of the Left Auricle*, *Trans. Clin. Soc. London*, 1904, 37, 192.
10. Virchow: *Bericht ueber das Leichenhaus des Charite-Krankenhauses*, *Charité-Annalen*, 1881, 6, 663.
11. Robin: *Sur un cas de myxome du cœur*, *Arch. de méd. exp. et d'anat. path.*, 1893, 5, 802.
12. Gairdner: *Case of Obstruction of the Right Auriculoventricular Orifice*, *Edinburgh Hosp. Rep.*, 1893, 1, 221.
13. Prudhomme, quoted by Link, reference 3.
14. Fraenkel, quoted by Link, reference 3.
15. Beck and Thatcher: *Spindle-cell Sarcoma of the Heart*, *Arch. Int. Med.*, 1925, 36, 830.
16. Ingram: *Cancerous Heart (?) with Dilated Right Ventricle*, *Phil. Med. Times*, 1878, 8, 259.
17. Armstrong and Moenekeberg: *Herzblock bedingt durch primaeren Herztumor*, *Deutsch. Arch. f. klin. Med.*, 1911, 102, 144.
18. Wolbach: *Congenital Rhabdomyoma of the Heart*, *J. Med. Res.*, 1907, 11, 495.
19. Moenekeberg: in Henke and Lubarsch's *Handbuch der speziellen pathologische Anatomie*, Berlin, 1924, 2, 507.

ANALYSIS OF NINE HUNDRED AND EIGHTEEN CASES OF BACILLARY DYSENTERY TREATED WITH SPECIFIC SERUM.

By PEDRO T. LANTIN, M.D., D.T.M.,

ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF THE PHILIPPINES MANILA, P. I.

(From the Department of Medicine, College of Medicine, University of the Philippines and the Clinics of the Philippine General Hospital.)

THERE seems to be a difference of results in the observations of investigators regarding the efficacy of serum therapy in bacillary dysentery. The writer shall present the results of his investigation and study along the same lines among Filipinos with the aim in view of clarifying the results of this particular treatment.

The materials are gathered from the clinical records of all dysentery cases (bacillary) admitted to the Philippine General Hospital since its establishment on September 10, in 1910, up to December 31, 1927 inclusive, a span of over seventeen years.

The total number of cases studied in this investigation is 2259, of which 1341 did not have serum administration while 885 received intramuscular injection of serum in varying amounts and 33 cases were given serum per rectum (retained enema).

In the serum treatment of bacillary dysentery, we must take into consideration several factors, the most important of which are: (1) The correctness of the diagnosis; (2) the severity of the epidemic; (3) the prevalence of other diseases; (4) the potency of the serum; (5) the age of the patient; (6) the duration of the illness before treatment; (7) and the amount of the serum given.

1. *Correctness of Diagnosis.* Correct diagnosis is the fundamental basis of all treatment. In case of bacillary dysentery it is necessary not only to make a correct diagnosis, but also to establish the diagnosis as early as possible, especially in children. Cases of bacillary dysentery are generally severe in children due to low powers of resistance of the body to the toxins. Consequently we should not lose time at the expense of the life of the patient in waiting for the confirmatory bacteriologic results of the stools, because in very many instances, by the time the physician is called, the disease has already progressed so far, that the treatment becomes less effective, if not a complete failure. Early clinical symptoms of bacillary dysentery like high fever, frequent bowel movements, diarrheic, mucoid, or bloody stools, dehydration, convulsions, and nausea and vomiting may not all be present when the patient is seen, but the presence of abundant pus cells and macrophages in the stools are strong indications of bacillary dysentery infection, and this examination can be done in a few minutes.

2. *Severity of Epidemics.* As a rule in all epidemics the deciding factor in the ultimate outcome of the disease is the type and virulence

of the infecting organism as well as the resistance of the patient. In bacillary dysentery, the Shiga-Kruse type is usually very toxic, while the Flexner group is generally mild. Hence the prevalence of one type of the organisms will greatly modify the results of the treatment. However, the Flexner type should not prejudice the physician, because in some cases it is severe and may end fatally.

3. *Prevalence of Other Diseases.* Bacillary dysentery like other diseases is influenced by the presence of other epidemics. In those which later on develop measles, diphtheria, influenza, etc., the efficacy of serum treatment is highly modified.

4. *Potency of the Serum.* The serum used in the treatment of bacillary dysentery should be adequately prepared. It must be a fresh product or at least be used within the limit of its prescribed effectivity. Is it not probable, then, that in some instances, the failure of serum therapy in the disease may be due to defective serum?

The serum from the Bureau of Science in Manila, Philippine Islands, is used in the treatment of the cases reported in this article. It is prepared as follows:

The cultures used for the preparation of curative antidysenteric serum by the Bureau of Science were isolated some years ago in Manila during a service outbreak of dysentery. Their antigenic property is well known.⁵ Both types, Shiga and Flexner were used in the preparation of the serum.

The cultures are killed at 60° C. for one hour and are injected subcutaneously to horses at weekly intervals. The doses of the injections are increased usually to 60 or 100 slants at one injection. After the last injection the serum is tested by means of agglutination and antitoxin test. One-tenth cubic centimeter usually neutralizes smoothly sure minimal lethal dose of dysenteric toxin in rabbits by intravenous injection. The horses are bled not sooner than one month after the last injection. The serum is then carbolyzed to contain 0.5 per cent phenol, then it is filtered and tested for sterility, safety and specific properties.

5. *Age of the Patient.* The percentage distribution of the cases by age is shown in Table I. Out of a total of 2259 cases, 1140 are children from under one year to five years of age, constituting 51.2 per cent. As age advances, the number of cases diminishes, more particularly after third decade of life.

If the cases studied are arranged into series of serum and non-serum groups, distributed by age, as shown in Table II, we shall find that the fatality rate in both is greater in children than in the adults.

The fatality is high in children due to the low powers of resistance of the body to the toxins. Age modifies, therefore, the outcome of the disease.

The low fatality in middle life is probably due to the immunity

acquired against the diseases but there is a limit to immunity. In old age there is a marked diminution of immunity and a weakening of the vitality. Hence the fatality rate is slightly increased.

TABLE I.—PERCENTAGE DISTRIBUTION OF DYSENTERY CASES BY AGES.

Age (years).	Distribution.	
	Number.	Per cent.
Under 1	299	13.5
1 to 5	841	37.7
6 to 10	208	9.3
11 to 15	97	4.4
16 to 20	199	8.9
21 to 30	338	15.2
31 to 40	113	5.1
41 to 50	53	2.4
51 to 60	43	1.9
61 to 70	20	0.9
71 and over	15	0.7
Total	2226*	100.0

* The 33 cases treated with retained enema are not included.

Table II shows the beneficial effect of serum treatment. The fatality among the cases without serum was 36.3 per cent as compared to 19.7 per cent among the cases treated with serum. It might however be asked, why, in spite of serum treatment, the fatality rate in the fourth decade of life is almost twice as high among those with serum treatment, as that in the case of the nonserum series of the corresponding age. This might be explained by the fact that very many of the cases treated with serum in adults were those of the very serious types, the mild ones, as a rule, were not submitted to specific serum treatment.

6. *Duration of Illness Before Treatment.* In the treatment of any disease the time factor is very important. The earlier they are treated the better are the cases' chances of recovery. This becomes more striking and significant in those diseases like bacillary dysentery, diphtheria, tetanus, etc., where specific therapy is indicated. Table III demonstrates that the earlier the serum is administered the less is the case fatality and the later it is given the higher the fatality. In this same table it is also shown a nonserum group receiving only medicinal treatment. The fatality rate among them also increases as the duration outside before treatment is longer. But, if the nonserum group is compared with the serum group the difference in the fatality rate is quite marked.

The low fatality rate in the early stages of the disease in the serum group may be explained by the well-known immunologic changes. In bacillary dysentery the bacilli produce toxins which can combine with the tissues of the body. The moment the union between poison and tissue is effected, it will be impossible to separate them. Once the combination is effected there is no known means of separating again the toxins and tissues that have been united firmly in wedlock.

with serum.

OUTCOME OF BACILLARY DYSENTERY

TABLE II.—OUTCOME OF BACILLARY DYSENTERY CASES IN VARIOUS AGES WITH AND WITHOUT SERUM.																					
Age (years).	Without serum.										With serum.										
	Definite termination.					Undetermined ending.					Definite termination.					Undetermined ending.					
	Recovered.			Died.	No. cases.	Improved.			No. cases.	Recovered.			Died.	No. cases.	Improved.			No. cases.	Undetermined.		
	No. cases.	Num-ber.	Per cent.			Num-ber.	Per cent.	Num-ber.		Per cent.	Num-ber.	Per cent.			Num-ber.	Per cent.	Num-ber.		Per cent.	Num-ber.	Per cent.
Under 1	163	68	41.7	95	58.3	81	57	70.5	24	29.5	32	18	56.2	14	43.8	23	15	65.2	8	34.8	
1 to 5	387	194	50.1	193	49.9	200	141	70.5	59	29.5	162	108	66.7	54	33.3	92	67	72.8	25	27.2	
6 to 10	87	60	69.0	27	31.0	30	26	86.6	4	13.4	71	43	60.6	17	23.9	20	18	90.0	2	50.0	
11 to 15	38	32	84.2	6	15.8	8	5	62.5	2	50.0	51	43	84.3	8	15.7	4	2	50.0	1	20.0	
16 to 20	66	63	95.4	3	4.6	22	17	77.3	5	22.7	167	151	90.4	16	9.6	5	21	87.5	3	12.5	
21 to 30	125	118	94.4	7	5.6	16	13	81.2	3	18.8	41	34	82.9	7	17.1	6	4	66.7	2	33.3	
31 to 40	49	45	91.8	4	8.2	2	1	50.0	1	50.0	24	20	83.3	4	16.7	3	3	100.0	0	50.0	
41 to 50	21	17	80.9	4	19.1	6	5	83.3	2	16.7	16	10	62.5	6	37.5	3	2	50.0	2	0.0	
51 to 60	18	10	55.6	8	44.4	3	1	33.3	0	0.0	9	5	55.6	1	44.4	0	0	0.0	0	0.0	
61 to 70	9	6	66.7	1	11.1	2	2	100.0	0	0.0	560	80.3	137	19.7	188	142	75.5	46	24.5		
71 and over	4	3	75.0	1	25.0	2	2	100.0	0	0.0	697	270	72.2	104	27.8	19.7	188	142	75.5	46	24.5
Totals	967	616	63.7	351	36.3	374	270	72.2	104	27.8	697	560	80.3	137	19.7	188	142	75.5	46	24.5	

Totals

NOTE.—The cases under "denied" improved or unimproved left the hospital improved.

TABLE III.—OUTCOME OF BACILLARY DYSENTERY CASES WITH AND WITHOUT ANTIDYSENTERIC SERUM IN RELATION TO DURATION OF ILLNESS PRIOR TO SERUM ADMINISTRATION.

Duration.	With serum.										Without serum.									
	Definite termination.					Undetermined ending.					Definite termination.					Undetermined ending.				
	Recovered.		Died.		Total.	Improved.		Unimproved.			Recovered.		Died.		Total.	Improved.		Unimproved.		
	Num- ber.	Per cent.	Num- ber.	Per cent.		Num- ber.	Per cent.	Num- ber.	Per cent.	Num- ber.	Per cent.	Num- ber.	Per cent.	Num- ber.		Per cent.	Num- ber.	Per cent.	Num- ber.	Per cent.
Within 24 hours	98	94	95.9	4	4.1	32	25	78.1	7	21.9	53	39	73.6	14	26.4	22	16	72.7	6	27.3
Two days	85	76	89.4	9	10.6	21	17	80.9	4	19.1	47	38	80.8	9	19.2	15	11	73.4	4	26.6
Three days	92	77	83.7	15	16.3	22	19	86.4	3	13.6	91	72	79.1	19	20.9	28	24	85.7	4	14.3
Four days	102	86	84.3	16	15.7	20	15	75.0	5	25.0	70	48	68.6	22	31.4	31	25	80.6	6	19.4
Five days	57	47	82.4	10	17.6	11	6	54.5	5	45.5	78	50	64.1	28	35.9	17	14	82.4	3	17.6
Six days	35	27	77.1	8	22.9	4	2	50.0	2	50.0	45	34	75.5	11	24.5	6	2	33.3	4	66.7
Seven days and over	150	89	59.3	61	40.7	67	49	73.2	18	26.8	461	252	54.7	209	45.3	224	157	70.1	67	29.9
Undetermined duration	78	64	82.1	14	17.9	11	9	81.8	2	18.2	122	83	68.0	39	32.0	31	21	67.8	10	32.2
Totals	697	560	80.4	137	19.6	188	142	75.6	46	24.4	967	616	63.7	351	36.3	374	270	72.2	104	27.8

NOTE.—The cases under "definite termination" have left the hospital either recovered or died, while those under "undetermined ending" have left the hospital improved or unimproved and we did not know whether they have recovered or died outside.

The damage is already done and it cannot be undone. The antiserum that is given is essentially only preventive and not curative. It will neutralize only the toxins that are free in the body at the time of its administration, hence the urgent necessity of administering the serum early and promptly.

7. *The Amount of Serum Given.* In serum therapy the right dosage is of utmost importance. It is not advisable to give only a small amount of antiserum, as it may not be sufficient to check the progress of the disease and there is much danger of losing the patient. If administered with proper precaution, especially if given intramuscularly, a large amount seldom produces untoward effects to the patient while he gets the benefit of a better resorption. In fact the writer's experience is that it is better to saturate the patient with serum in the first two or three days of the treatment. However, if after administering big amounts of antiserum for three or four days no improvement is noted, it is his practice to discontinue the serum because we cannot expect any satisfactory results.

As a necessary precaution against severe immediate reactions or anaphylaxis, the writer is following the common practice of injecting first 1 cc. of the serum and one hour later if no untoward reaction occurs, the necessary amount is administered all at once. One-half cubic centimeter of 1 to 1000 solution of adrenalin by hypodermic route as a further preparation for serum injection may also be given.

In the table on p. 641 are shown the comparative effects of different amounts of serum given intramuscularly. It is evident that the greater the amount of the serum administered the less is the fatality rate. The best results seem to have been obtained with the administration of between 51 to 150 cc. of antiserum. This has been given intramuscularly in 20-cc. doses three times daily for two or three days. The same doses were given to adults and children.

The results from 151 cc. of serum and over are somewhat misleading because of wide fluctuations. This may be explained by the fact that the cases under this item were few. Besides this, the majority of them were cases falling under the category of those that would not respond in any way to serum administration. Moreover, many of them were long-standing cases.

It is interesting to note that even the cases with "undetermined endings" were seemingly benefited by the serum treatment, and the greater the quantity of serum given the better the results.

Various Methods of Serum Administration. Antiserum may be administered in various ways, such as the intramuscular, intravenous per rectum (retained enema) and their combinations. The most common is the intramuscular injection. It is not necessary to describe here the procedure in intramuscular and intravenous injections because everybody is familiar with these methods. Serum administered per rectum (retained enema) is a new method of treat-

TABLE IV.—EFFECTS OF DIFFERENT AMOUNTS OF SERUM IN DYSENTERY CASES.

	Definite termination.						Undetermined ending.			
	Total. No. cases.	Recovered.		Died.		Total. No. cases.	Recovered.		Died.	
		Number.	Per cent.	Number.	Per cent.		Number.	Per cent.		
5 to 10 cc. serum	76	49	64.4	27	35.6	26	16	61.5	10	38.5
11 to 20 cc. "	131	104	79.4	27	20.6	36	26	72.2	10	27.8
21 to 50 cc. "	246	203	82.5	43	17.5	76	58	76.4	18	23.6
51 to 100 cc. "	152	130	85.5	22	14.5	34	28	82.4	6	17.6
101 to 150 cc. "	46	39	84.8	7	15.2	8	8	100.0	0	0.0
151 cc. serum and over	46	34	73.9	12	26.1	8	6	75.0	2	25.0

NOTE.—The cases under "definite termination" have left the hospital either recovered or died, while those under "undetermined ending" have left the hospital improved or unimproved and we did not know whether they have recovered or died outside.

ing bacillary dysentery which the writer has been using since the year 1917. Favorable results were published in 1918² and was followed by a second report on the same subject in 1921.³ The writer's recent observations on this method of treatment confirm his previous findings concerning this manner of serum administration (retained enema alone).

The original method of serum administration per rectum consists in the introduction of the serum through a long rubber tube, one end of which is provided with a funnel. The patient is placed in the knee-chest position. The serum is given high and retained as long as the patient can possibly do it, the longer the better. Before the serum is given the patient is prepared for it. The preliminary preparation consists in giving a cleansing enema of sodium bicarbonate (1.5 per cent), followed afterward by another enema of 60 to 100 cc. of starch solution with 15 drops of laudanum, so as to diminish the irritability of the intestine. The high serum enema is given a half hour after the starch enema.

There are several disadvantages of the original method mentioned above. It is a gravity method which is quite hard to do in case of children because they usually cry and resist the procedure, thereby increasing the intraabdominal pressure often with failure to introduce the serum. Another disadvantage is the inadvisability of giving opium preparations in children. In order to retain the enema it is necessary to give small amounts of serum at frequent intervals, but a large portion of the serum sticks to the container and the rubber tube while big amounts of serum if given at once will have a tendency to be expelled immediately. Furthermore, the original method requires a trained person to administer the serum.

The method of serum administration per rectum, as now employed by the writer, is more simple than before. Instead of the gravity method I am forcing the serum by the syringe which is attached to one end of a rubber catheter lubricated with vaseline. This method does not produce any discomfort to the patient and can be given even when the child is asleep without waking him up. Any ordinary person can give this method of treatment.

It is to be taken into consideration that serum administration is difficult in children specially if they are awake because they usually resist the treatment. Children are less obedient to instructions. Most of the patients however, both adults and children, prefer the serum enema because this method is not painful.

In adults with very frequent bowel movements it is beneficial to give 5 to 10 cc. of elixir paregoric *per os*. This will diminish the intestinal peristalsis of the intestines and hence the serum is properly retained. The elixir paregoric is given fifteen to thirty minutes before serum administration.

Lately, the writer treated 33 cases of bacillary dysentery by serum enema alone. Their distribution by age is shown in Table V.

TABLE V.—AGE DISTRIBUTION OF BACILLARY DYSENTERY CASES TREATED BY SERUM ADMINISTERED PER RECTUM (RETAINED ENEMA).

Age (years).	Total cases.	Recovered.		Died.	
		Number.	Per cent.	Number.	Per cent.
Under 1	0	0	0	0	0
1 to 5	11	11	100	0	0
6 to 10	0	0	0	0	0
11 to 15	0	0	0	0	0
16 to 20	6	6	100	0	0
21 to 30	12	12	100	0	0
31 to 40	1	1	100	0	0
41 to 50	1	1	100	0	0
51 to 60	0	0	0	0	0
61 to 70	1	1	100	0	0
71 and over	1	1	100	0	0
Grand total	33	33	100	0	0

The majority of these 33 cases however were not serious. The general condition was good. The fever was not very high and the bowel movements varied from 8 to 25 in twenty-four hours. Many of the cases were treated early. The results were very encouraging and all of the cases recovered.

In adults the amount of serum administered per rectum is 20 to 30 cc. every four hours. Sometimes in mild cases one or two administrations are sufficient, more specially in early cases. In children the author usually gives one-half of the adult dose because large amounts tend to be expelled at once. If the amount is not properly retained it is repeated immediately without any danger. The serum should not be diluted because the big bulk will irritate the intestines and produce untimely peristalsis, causing it to be expelled at once.

Discussion. Bacillary dysentery is one of those specific diseases which produce definite pathologic lesions. The toxins elaborated by the bacteria act locally in the large intestines, producing typical ulcerations. When absorbed, the toxins produce varying degrees of toxemia which may affect the nervous system and other vital organs. The injections of dysenteric toxins as observed by Flexner and Sweet, and Doerr produce symptoms and anatomic changes in the large intestines of experimental animals similar to those found in human beings.¹ Doerr in his experiments was also able to save the animals from the effects of a lethal dose of toxin by previous injections of antitoxin. Similar results were reported by Todd, Vaillard and Dopter.¹

Shiga, the pioneer worker in bacillary dysentery, states that anti-dysenteric serum is bactericidal as well as antitoxic.⁶ This view was supported by Sandwith, who gave the same opinion that the serum of dysentery is both antitoxic and bactericidal.⁴

The fundamental principle of serum treatment in bacillary dysentery is based on the above facts, theories, and conclusions that were verified by experimentations on the part of reliable workers. It will not therefore be out of place to use the anti-dysenteric serum as retained enema. This method of treatment, the writer believes, is not unscientific. Where can we better combat the bacteria and their toxins, than in the very place where they are lodged and produced? To his mind the direct attack on the causative agent and its poison is the best means of fighting a disease.

In the treatment of bacillary dysentery, the writer used serum administered per rectum (enema). In this way the antiserum gets direct access to the bacteria and its toxins present in the intestines. There it can act both as "antitoxic and bactericidal." In the intestines absorption takes place also, and once in the circulation, the antiserum can neutralize the free toxins.

The principle involved in the intramuscular and intravenous injections is the neutralization of the toxins in the body. In the rectal administration (enema) this principle also holds true. But, as the writer stated, the per rectum administration possesses the advantage of acting immediately and directly in the intestines. In intravenous injection the serum is introduced directly into the circulation. Absorption must take place in the muscles when the serum is given intramuscularly, and if the serum is administered per rectum, absorption takes place in the intestines.

The writer's experience with serum administration per rectum (enema), was very encouraging, several notable clinical changes in the patient having been observed, provided that the serum was properly retained and administered early. After twenty-four hours the patient experiences general improvement of the subjective symptoms. The colicky pain is greatly diminished; the stools decrease in number; the temperature goes down. Later on, the stools gradually become less bloody and less mucoid; they become fecal and soft, and finally normal. In early diagnosed cases where serum was given at once per rectum (enema) the stools did not have a chance to become bloody.

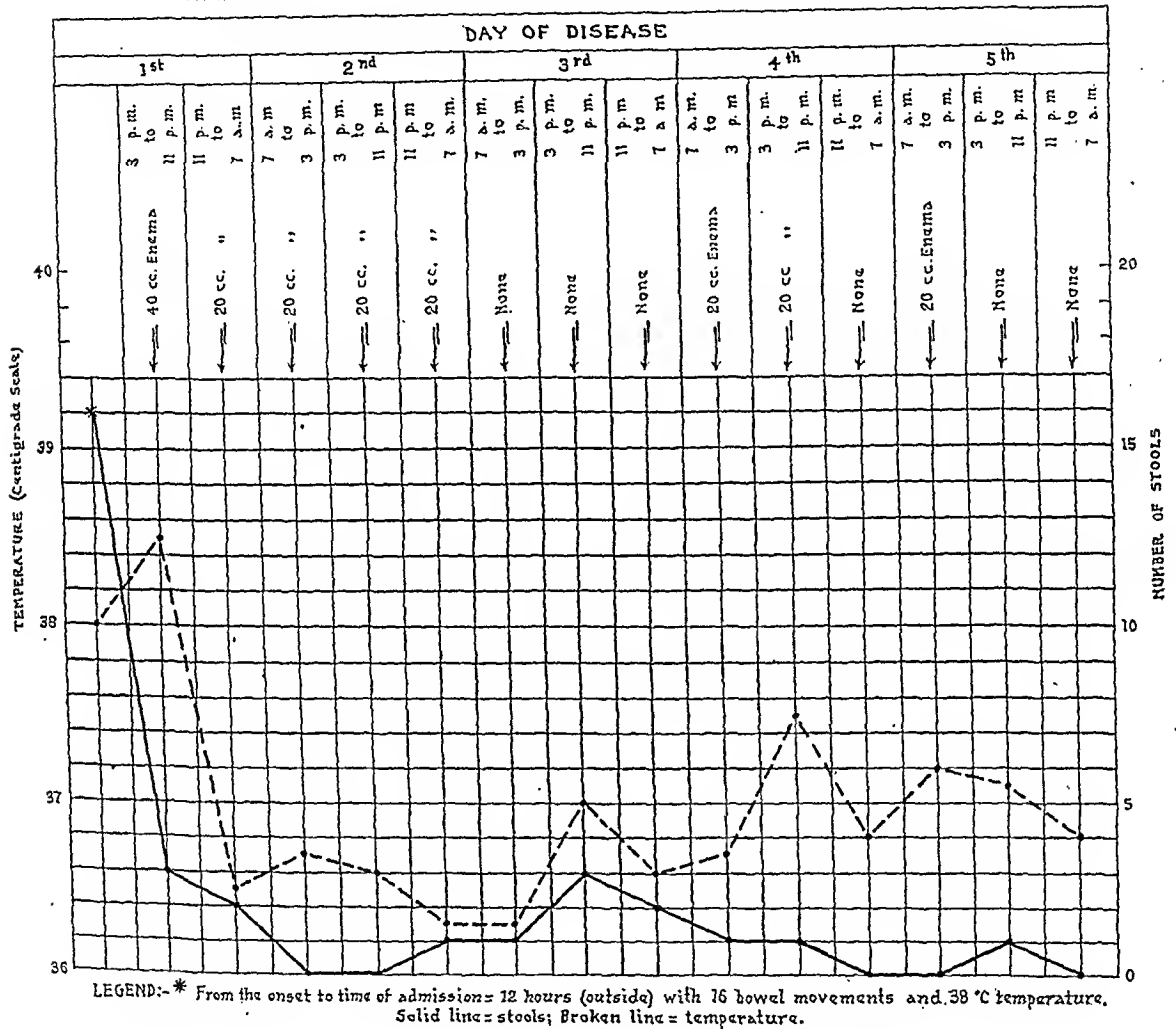
Graph I illustrates the marked effects of serum administered per rectum (enema).

All the 33 cases treated with serum enema alone it is true were apparently mild from the beginning. It is a clinical fact, however, that very many cases of bacillary dysentery start with mild symptoms, becoming serious after some time. Is it not, then, an achievement in the treatment if the disease could be kept mild throughout its course?

The writer has encountered in his practice cases in which serum enema did not produce the desired result as shown in Graph II. This was found to be due to improper retention of the serum in the intestines. Intramuscular injection, combined with serum

enema gave, in these cases, a highly satisfactory result. This method is, in the opinion of the writer, a very desirable procedure in the groups of cases above mentioned. The intramuscular injection is discontinued once the bowel movements have markedly decreased because the patients prefer the painless route, through the rectum. Continuance of the serum enemata in the early convalescence period is preferred.

GRAPH 1. EFFECT OF SERUM ADMINISTERED BY RETAINED ENEMA METHOD

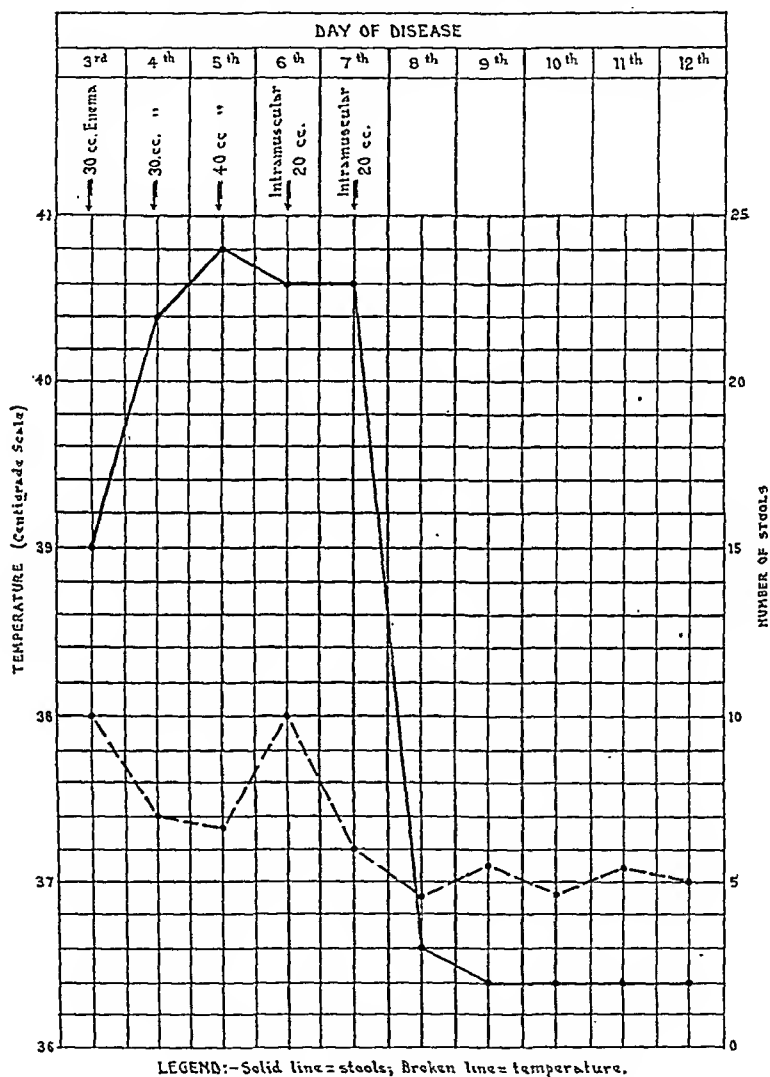


Some patients are highly susceptible to serum injection of any kind. In cases of this nature the use of serum enemata becomes very necessary. Even the preliminary test injections of small amounts of serum do not prevent at times the occurrence of serious complications (see complications, Case V). But the rectal administration has not produced so far anaphylactic shock or severe immediate reactions, besides the patient is saved from the inconvenience of pain. There are patients who develop urticarial manifestations immediately following intramuscular injections of serum. In such cases the method of treatment by injections was discontinued and,

instead, serum per rectum (enema) was employed without any bad effect.

The intravenous injection is employed in very severe cases. A few hours after injection there is marked alleviation of the symptoms; pulse becomes full and strong; restlessness diminishes and the general appearance becomes brighter in the next twenty-four

GRAPH 11. EFFECT OF ANTIDYSENTERIC SERUM ADMINISTERED BY THE COMBINED METHODS
(RETAINED ENEMA AND INTRAMUSCULAR INJECTION)



hours. The intravenous administration of serum is usually accompanied with chills or chilly sensation which may last for thirty minutes followed by rise of temperature.

Some cases of bacillary dysentery that are apparently mild die of the disease soon after serum administration. This is seemingly paradoxical. It is not astonishing to see severe cases terminating fatally, but mild ones resulting in death are perplexing. It is very

difficult to explain this phenomenon satisfactorily. It is known that minimum lethal doses of bacterial toxins do not produce instantaneous death in experimental animals as do chemical poisons, like alkaloids, for instance. Bacterial toxins have to pass a certain length of time before they can produce much damage in the tissues—that is, before the symptoms appear. Therefore, apparently mild cases do not necessarily mean that the toxins are still free in the circulation, but might be bound already to the tissues and the case might appear mild, because the effect of the toxin is still in the incubation period.

Complications Resulting from the Treatment. The cases that have developed special complications as a result of serum administration are very few and they will be discussed briefly in this report.

Case Abstracts. **CASE I.**—A male, aged thirty-two years, strong and robust. He was given two intramuscular injections of serum, 20 cc. each at twenty hours' interval. One hour after the second injection the patient became weak, and restless with subnormal temperature. The pulse was small and rapid, with cold perspiration and the respiration increased in rate. The patient was given 1 cc. of 1 to 1000 adrenalin injection subcutaneously but he died twenty-four hours after the onset of these symptoms. No autopsy was made.

CASE II.—A female nurse, aged twenty-five years, fairly developed and strong. She was receiving 20 cc. of serum intramuscularly every day for four days but on the eighth day of the disease she developed urticarial rash all over her body. It was accomplished by sudden rise of temperature, and pain was so severe that she could hardly open her mouth, and could hardly move her extremities. She recovered with salicylate treatment and adrenalin injections.

CASE III.—Another female nurse, aged twenty-one years, well-developed, strong and robust. She was given a daily intramuscular injection of 20 cc. of serum. Two and a half hours after the fourth injection she became very weak, restless and moaning continuously, subnormal temperature, cold clammy perspiration with weak and rapid pulse. She remained in this condition for twelve hours, after which she gradually recovered after 1 cc. of 1 to 1000 adrenalin was given subcutaneously.

CASE IV.—A male child, aged two years and three months, well-developed and strong. One year previously he received two subcutaneous prophylactic injections of sensitized antidysenteric vaccines (polyvalent). The first prophylactic injection contained 200,000,000 bacteria. Twenty-four hours later the child had a slight rise of temperature which lasted for twelve hours. Three days after the first prophylactic injection he was given another dose of 400,000,000 bacteria. Twelve hours later this was followed by high fever accompanied by bloody and mucoid stools. This condition lasted for twenty-four hours and the number of bowel movements was five. The feces was examined microscopically and numerous pus cells and macrophages were found but bacteriologically negative for dysentery bacilli. As soon as the result of the microscopic examination of the feces was known, 10 cc. of serum was given three times a day per rectum (enema). The next day the patient was greatly improved and soon returned to normal condition. Very recently, about one year since the first prophylactic injection, the child developed dysenteric symptoms with pus cells and macro-

TABLE VI.—THE EFFECTS OF THE DIFFERENT METHODS OF SERUM ADMINISTRATION IN THE TREATMENT OF BACILLARY DYSENTERY.

Treatment.	Termination.						Undetermined ending.						Grand total..
	Recovered.		Died.		Total cases.	Improved.		Unimproved.		Total cases.			
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.			
Without serum	616	63.7	351	36.3	967		270	72.3	104	27.8	374	1341	
Serum intramuscularly	560	80.3	137	19.7	697		142	75.5	46	24.5	188	885	
Serum per rectum (enema)	33	100.0	0	0.0	33		0	0.0	0	0.0	0	33	
Totals	1209		488		1697		412		150		562	2259	

phages in the stools. One cc. of antidysenteric serum was immediately injected intramuscularly. No reaction was observed from the injection. One hour later 19 cc. of serum was given intramuscularly. This was followed after two hours by accelerated serum reaction, that is itching reddish macules on the ears followed by similar eruptions on the face, neck, body and lower extremities and twelve hours after the whole body was swollen but not edematous. The child urinated frequently, almost once every hour. Urine examination was negative for casts and showed only slight amount of albumin. No further injection of serum was given but 10 cc. of serum was administered every four hours per rectum until three doses were given. The serum enema was given four hours after the onset of the complications. The patient recovered quickly. Ten days after the apparent complete recovery, the child was given yolk of an egg and a few hours after, the child developed again severe urticarial rashes all over the body and after twenty-four hours the whole body was again swollen without edema but he urinated less frequently at this time, three times in twenty-four hours. Urine examination was again negative for casts and showed only slight amount of albumin. Adrenalin and calcium chlorid were given by mouth. On the third day the patient began to recover rapidly.

CASE V.—A female, aged fifty years, fairly nourished, was given an intramuscular injection of normal horse serum in 1917 due to metrorrhagia. In 1927 the patient contracted bacillary dysentery. She was then given 0.5 cc. of antidysenteric serum subcutaneously. One hour later 1 cc. was given, and after one more hour, 18.5 cc. of the serum were given intramuscularly. For four days the patient received 20 cc. of the serum intramuscularly three times a day. On the eighth day of the disease the patient became cyanotic with symptoms of collapse which remained for several hours. She was then given adrenalin subcutaneously and calcium chlorid *per orem*. The patient recovered.

CASE VI.—A female child, aged two years, fairly developed and strong. She developed dysentery (bacillary) and was injected intramuscularly with 20 cc. of antidysenteric serum every twelve hours for three days. Five days after the last injection urticarial rashes appeared. The patient recovered after adrenalin treatment *per orem*.

CASE VII.—A male child, aged three years, well-developed and robust. The patient developed symptoms of bacillary dysentery. He was given 20 cc. of antidysenteric serum intramuscularly every twelve hours for three days. Three days after the last injection the patient had urticarial rashes. The case recovered after adrenalin was administered.

Conclusion. From the record of the 2259 cases of bacillary dysentery that the writer has studied, it is observed that serum treatment is in general effective.

From Table VI we note the encouraging results obtained from serum administration per rectum (enema), but it is still untimely to give a very definite conclusion regarding the absolute efficacy of this method on account of the limited number of cases treated. The results, however, are very encouraging.

NOTE.—The author is grateful to Drs. Luis Guerrero, Otto Schöbl and Hilario Lara for their valuable suggestions; to Dr. Jose Albert for permission to include in this investigation the cases in pediatrics; and to the staff of the Department of Medicine for their coöperation.

REFERENCES.

1. Doerr, R.: In Kraus und Levaditi, Handbuch der Technik und Methodik der Immunitäts-forschung, Gustav Fischer, Jena, 1909, 2, 164.
2. Lantin, P. T.: Philippine J. Sci., Sec. B, Trop. Med., 1918, 13, 261.
3. Ibid., 1921, 19, 629.
4. Sandwith, F. N.: Lancet, 1914, 2, 637, 683, 731, 783.
5. Schöbl and Villamil: Philippine J. Sci., 1926, 30, 1.
6. Shiga, K.: Modern Medicine, Osler, W., and McCrae, T., 2d ed., Philadelphia, Lea & Febiger, 1913, p. 766.

BACTERIAL HYPERSENSITIVITY OF THE INTESTINAL TRACT.

ITS TREATMENT WITH AUTOGENOUS VACCINE AND SODIUM RICINOLEATE.

BY STANLEY E. DORST, A.B., M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF CINCINNATI,

AND

ROGER S. MORRIS, A.B., M.D.,

TAYLOR PROFESSOR OF MEDICINE, UNIVERSITY OF CINCINNATI.

(From the Department of Internal Medicine of the University of Cincinnati and the Kuhn Diagnostic Laboratory of the Cincinnati General Hospital.)

OVER a period of three years we have been interested in a type of chronic disease which has presented a clinical picture varying within very wide limits. Chronic appendicitis, peptic ulcer, chronic cholecystitis, spastic colitis and mucous colitis are frequent diagnoses and, unfortunately, often the patient goes at once to the surgeon to have his appendix removed or his upper abdomen explored only to continue with symptoms unchanged after the operation. Or again, after an exhaustive and expensive diagnostic study the internist finds no definite evidence of an organic lesion, the only fairly consistent physical finding being a spastic distal colon. A diagnosis of nonulcerative colitis or irritable colon with "autointoxication" or of mucous colitis is often made, or perhaps the symptoms are assigned to an intestinal neurosis.

It is not our intention to go into the detailed symptomatology of these cases. Jordan and Kiefer¹ have recently presented an excellent clinical summary of what they chose to call the "irritable colon." It is our intention, however, to offer the results of a series of investigations aimed at finding a common cause for this varied symptomatology. In spite of the fact that bacteriologic studies had been made repeatedly, and that the conclusions were almost as numerous as the investigators, we felt that the only approach which would permit an entering wedge would be the bacteriologic approach and

one of us (D) determined once more to investigate the intestinal flora.

Here it is necessary to digress and state that for almost four years, along with several members of our laboratory staff, we have been trying to evaluate the importance of intradermal reactions when employed to indicate specific susceptibility to bacterial antigens. We have followed the technique described by Wherry, in 1927,² and further elaborated by Wherry and Dorst, in 1928.³ Over 300 patients have been studied, including cases of arthritis, sinusitis, bacterial asthma, ulcerative and nonulcerative colitis, certain skin infections and chronic cholecystitis. Though we are not yet in a position to form definite conclusions, we have evidence to support several generalizations. We read as a positive reaction one which reaches its height in twenty-four to thirty-six hours after injection, is characterized by induration, local heat and redness and is often associated with focal and general reactions. Such a skin reaction, we believe, from the study of hundreds of cases, justifies the following conclusions: (1) That the individual is susceptible to the organisms injected; (2) that his tissues have already been invaded by that organism; (3) that he has inadequate immunity to enable him completely to counteract its toxicity. There are exceptions to these statements, but in general they seem to hold and express in a rather simple way facts which would be hopelessly confused should we attempt to translate them into the terminology of the immunologist.

We believe that in many instances these reactions represent sensitization of the mucous membranes of the body to organisms which are frequently considered nonpathogenic. Using the term in its broad sense, one may speak of such reactions as allergic. Here we cannot go into a comprehensive survey of this work. Most of our results have been published. This brief review forms a necessary introduction to the present study. In our consideration of the bacterial flora of the gastroenteric tract we hoped to identify certain organisms with our clinical problem on the basis of positive intradermal reactions.

Originally we thought we might find some unusual organism in the enteric flora which could be shown to be the responsible agent, and wasted an entire summer searching for that organism. Careful bacteriologic studies were carried out. All the organisms which failed to fall into the catalogue of "normal flora" were cultured by aërobic, anaërobic and partial-tension methods. The strains were isolated in pure culture, heat-killed and used to make skin tests. The results were disappointing and most inconclusive; it was necessary to read the majority of our skin tests as negative, and there was no uniformity regarding the few positives. We found ourselves left with only the "normal flora."

We selected a group of 30 patients, all of whom had symptoms

of long-standing. Most of them had been subjected to the usual treatment for autointoxication, that is, had been given acidophilus milk, lactose and a diet, without the desired therapeutic result. They had already been studied bacteriologically as just outlined, and we now turned our attention to the normal flora. *Bacillus coli communior*, *Bacillus coli communis*, *Bacillus acidi lactici*, *Bacillus fecalis alkaligenes*, *Bacillus proteus*, *Bacillus cloacae*, *Bacillus mucosus capsulatus* were included in our group for study, along with the Gram-positive diplococcus, commonly known as *Streptococcus fecalis*. The occasional anaërobic spore-bearers which were recovered were eliminated, since spore-forming organisms do not lend themselves to intradermal injections. Our 30 patients were skin-tested in the usual fashion. The results were most astonishing: 26 of the 30 patients showed marked sensitivity to one or several of the "normal strains." *Bacillus coli communior* led the field, with *Bacillus communis* second, then *Bacillus mucosus capsulatus*, *Bacillus fecalis alkaligenes* and *Bacillus proteus* followed in the order named.

Many of these strains were markedly hemolytic when grown on blood media, and when injected intradermally the reactions produced were not only local but frequently focal and general. Oftentimes a typical gastroenteric attack with all the symptoms common in a given case would be precipitated by the inoculation. The statement has been made that all individuals will show marked symptoms when *Bacillus coli* strains are injected.⁴ It was necessary to investigate this statement, and all the patients on a medical ward who were not seriously ill were tested. Over 50 per cent of these patients chosen at random failed to show positive reactions to either exogenous or autogenous strains, and almost all of those who did react gave a history of gastroenteric disturbances. Again patients with tuberculous enteritis, acute ulcerative colitis and typhoid usually failed to give a positive reaction to the strains we were investigating.

Our next step was to attempt the desensitization of patients sensitive to "active" strains, and this was carried out by the usual method, giving exceedingly small doses at daily intervals, keeping always within the dose producing local or focal reaction. Some of these patients along with many others who have been added to the group have been treated with vaccine for months. The usual result was a gradual disappearance of skin sensitivity which was paralleled by a disappearance of clinical symptoms. It was slow work and required complete coöperation on the part of patients, but the results have been exceedingly gratifying. Contrary to our usual experience in attempting experimental work with patients, these people have not deserted us within a few weeks, but instead have, for the most part, been very faithful. The answer seems to be that after the first two weeks most of them were feeling better

FIG. 1

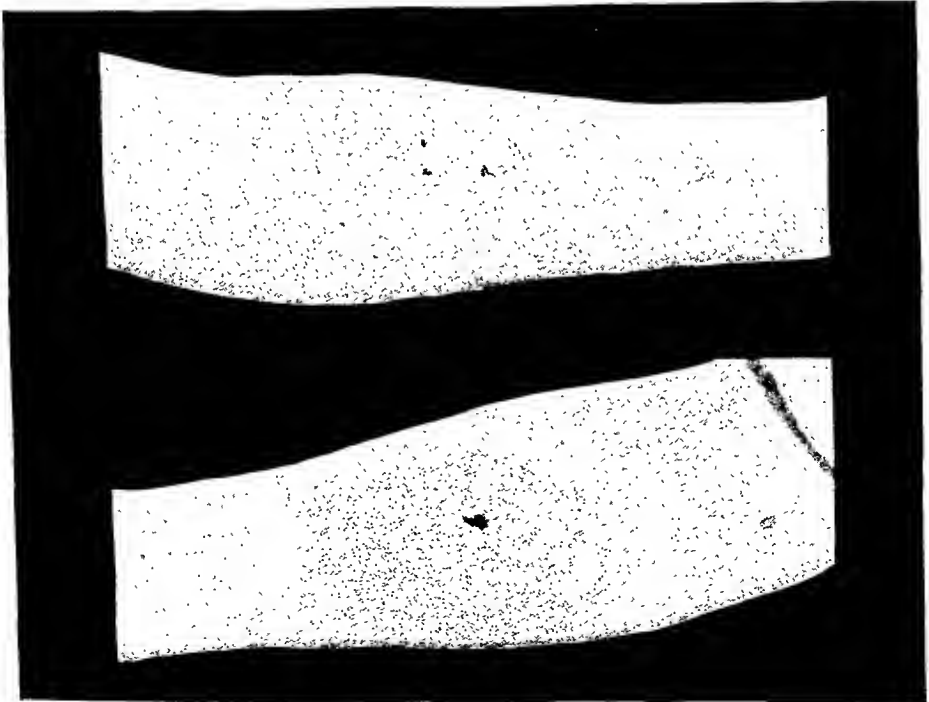
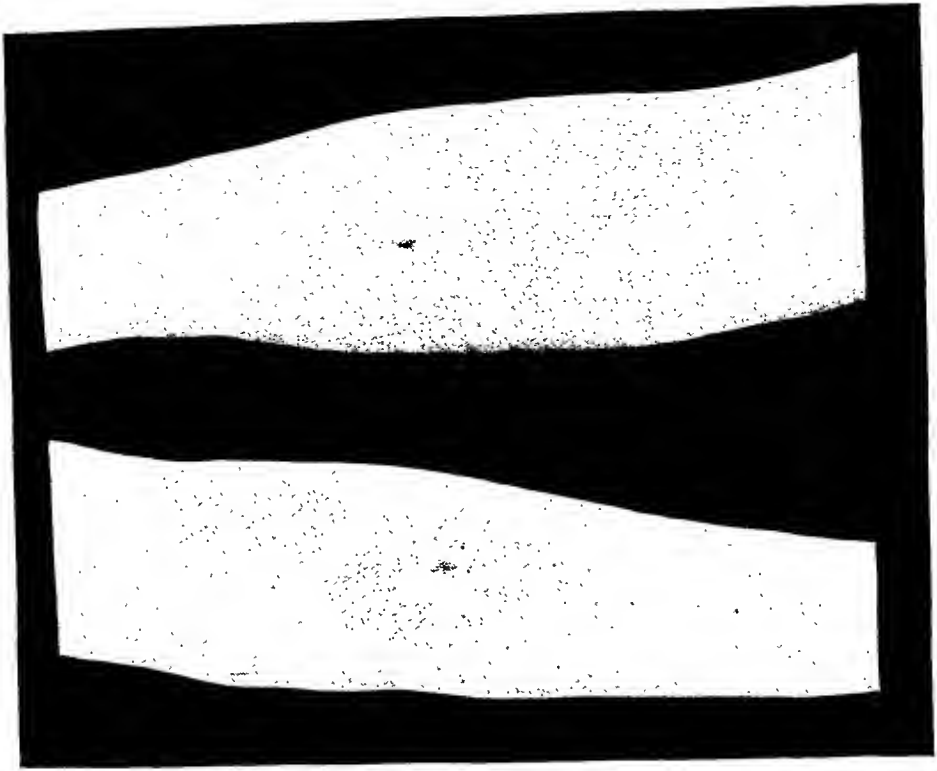


FIG. 2

FIGS. 1 and 2.—Detoxifying action of sodium ricinoleate upon organisms of enteric flora. The right and left arm in each case have received injections of the same organism. In Fig. 2 three injections were made, giving three times the dose of detoxified vaccine. No reaction resulted. The lower picture shows the marked reaction from the untreated suspension.

than they had for years. We studied a group of private, ambulatory patients and were able to follow over 70 cases. The symptoms completely disappeared in over 30 and there was marked improvement in the majority of the remainder.

Prior to our attempt to desensitize such patients, one of us (M) had been obtaining gratifying results in a certain group of similar cases by the use of repeated doses of castor oil. The routine consisted in having the patients take 0.5 to 1 ounce of castor oil each evening upon retiring. After the first forty-eight hours the cathartic action of the drug passed, and many so treated improved. The toxic symptoms disappeared, the colon became less spastic both on physical and Roentgen ray examination, tenderness, nausea and asthenia often lessened. The difficulty with such treatment lay in the fact that most individuals could tolerate castor oil for only a few days and very few could take it for weeks.⁵ We were interested to know whether the treatment with castor oil could be linked up with our sensitization studies. The improvement cannot be explained as being due to increased elimination, since the cathartic action of the oil is evanescent, and many patients so treated show a tendency to become somewhat constipated. The answer must be sought in the chemical action of the oil, which is changed to ricinoleates in the intestines. In using castor oil we had in mind Larson's work with sodium ricinoleate,⁶ and thought that this was the active principle involved, operating as a detoxifying agent.

Our next step was to determine whether or not sodium ricinoleate exerted a detoxifying action on the organisms which we had found capable of producing positive skin reactions in our patients. Heat-killed suspensions of the various strains were subjected to a concentration of 1 per cent sodium ricinoleate for twelve hours. The organisms were then packed and washed free of the ricinoleate. Simultaneous injections of untreated and treated strains were made in persons already shown to be sensitized to the normal flora. In each case we had achieved complete detoxification, as evidenced by the absence of skin reactions. Whereas the untreated suspensions produced violent reactions the detoxified strains gave rise to no local, no focal or general reaction. An individual who could not tolerate 0.15 cc. of the untreated suspension without marked local and general reaction could receive five times this dose of the detoxified vaccine without reaction. All the strains we have described, with the exception of the *Streptococcus fecalis*, could be so detoxified. (See Figs. 1 and 2, for illustration.)

We at once substituted detoxified vaccine for the untreated suspensions, and found the antigenic properties of the vaccine unimpaired. We then attempted to give sodium ricinoleate by mouth, but here we encountered difficulties, for the chemical proved to be exceedingly irritating. After various failures to find a satisfactory method of administration, the William S. Merrell

Company, of Cincinnati, working on the suggestion of Dr. Morris, solved the problem. Five grains of pure sodium ricinoleate were suspended in olive oil and enclosed in a soft enteric capsule. Such capsules seldom give gastroenteric symptoms, and most patients take them for months without discomfort. At first the patient is given a capsule before each meal and one at bedtime; gradually the dose is decreased as symptoms subside. The therapeutic effect is distinctly more marked than the best results secured with castor oil. Patients have been treated with detoxified vaccine alone, with ricinoleate alone and with both, and the combination has proved most effective. All other forms of treatment have been purposely omitted.

One very striking observation has been made, that patients who have been given sodium ricinoleate orally and no other treatment, gradually lose their skin sensitivity to organisms to which they had shown previous sensitization. This permits a very attractive speculation, that the ricinoleate acts on the organisms of the enteric tract in such a manner that a toxic body is converted into an antigen and autovaccination results. Such an explanation is quite in keeping with the recent work of Besredka. We have observed another interesting relationship. Only patients who show sensitization to organisms of their enteric flora are benefited by the administration of sodium ricinoleate.

Discussion. We are, in brief, trying to explain the clinical picture of "autointoxication," spastic or irritable colon and mucous colitis and the varied symptomology which such terms at once bring to the clinician's mind, on a scientific basis. Our experimental data, as just reviewed, and our clinical studies lead us to believe that the underlying factor in these conditions is a hypersensitivity of the enteric tract to certain bacteria. We also believe that the organisms most frequently responsible are those which have always been included under the heading, "normal flora." The hypersensitivity of the enteric tract results in local spasm of certain portions of the colon quite analogous to that which occurs in bronchiolar hyper-tonus (asthma), with ensuing constipation and a whole train of reflex aberrations which follow the interruption of the normal colonic rhythm. It would also seem that such hypersensitivity permits the absorption into the blood stream of large amounts of toxic products, resulting from bacterial metabolism, thence to the liver; when their concentration is sufficient to pass the threshold interposed by the detoxifying function of the liver they pass into the general circulation, giving rise to the clinical picture perhaps best recognized under the term, autointoxication.

This conception seems to warrant the assumption that we are dealing with intestinal allergy. A phenomenon which has occurred repeatedly in the course of our investigations lends considerable weight to this theory. In Case 27, a patient with symptoms of five

years' duration, 8 strains of organisms from the patient's own stool were injected intradermally. Of the 8, she showed marked skin sensitivity to 3; a hemolytic *Bacillus coli*, *Bacillus fecalis* alkaligenes and *Bacillus mucosus capsulatus*. The other 5 strains failed to produce skin reactions. This patient had been subject to recurring attacks characterized by abdominal cramps, constipation, marked abdominal distention, headache and profound prostration. These symptoms are given in the usual order of their development. Attacks would last two to four days and would frequently terminate with nausea and vomiting. During the attacks the distal colon was rigid, contracted and tender, while the proximal colon would be markedly distended. As a rule, four to six weeks would intervene between attacks, and during this period of remission undue fatigue on exertion was the only definite symptom. On the day following the intradermal tests our patient left Cincinnati for a six weeks' vacation in northern Michigan, to return feeling unusually well. We had prepared a vaccine from the "active" strains during her absence, which she declined to take because of her general state of wellbeing. Within a week following her return to normal routine she had a very severe attack with all the usual symptoms, and, to her amazement, at the sites of injection of the 3 active strains made six weeks before she developed reactions in every way similar to the original ones, with redness, induration and local heat. We saw these reactions, and they corresponded exactly to her primary reaction chart. Since then we have observed the same phenomenon on several occasions. After gradual desensitization, using a vaccine detoxified with sodium ricinoleate, her attacks faded out, and she has been practically free of them for eighteen months.

Our method of treatment by bacterial desensitization and detoxification, with possible autovaccination, using sodium ricinoleate orally, also suggests, because of its success, the allergic nature of the diseases. We would stress the importance of using small, frequently repeated doses when administering vaccine to such patients. We begin with a 1-minim dose, administered subcutaneously, and continue this dose for several days before increasing to $1\frac{1}{2}$ minims. Then the dose is slowly advanced by $\frac{1}{2}$ -minim amounts to 3 or 4 minims, using the local and general reaction as indication of overdose. After reaching 3 or 4 minims, the dose is held at this point, and often given for several months, the dermal sensitivity being the index of progress rather than the patient's freedom from symptoms. At first the injections are given daily, but after the dose has reached 3 minims they are given three times weekly. When detoxified vaccines are employed the dose may be increased more rapidly, but from time to time intradermal tests should be made with the original untreated strains in order to check the progress of desensitization.

Sodium ricinoleate given by mouth over a long period of time will

alone often achieve a satisfactory result with diminution of skin sensitivity, as described above, but we wish to repeat that our best results have been achieved by the combined use of detoxified vaccine and sodium ricinoleate administered orally.

Conclusion. 1. We feel that we have demonstrated a definite relationship between a well-recognized group of clinical symptoms and bacterial hypersensitization of the enteric tract.

2. This sensitization is revealed by intradermal reactions and suggests that the so-called "normal flora" is frequently found playing a decidedly abnormal rôle.

3. Desensitization by repeated small injections of the "active" strains results in both clinical improvement and a gradual disappearance of skin sensitivity.

4. Sodium ricinoleate detoxifies many organisms in the enteric flora *in vitro*, as demonstrated by the disappearance of skin reactions upon the injection of strains which before detoxification have given marked reactions.

5. There is worthy evidence to suggest that sodium ricinoleate administered by mouth exerts a detoxifying action on the enteric flora *in vivo*.

BIBLIOGRAPHY.

1. Jordan, S. M., and Kiefer, E. D.: J. Am. Med. Assn., 1929, **93**, 592.
2. Wherry, W. B.: J. Infect. Dis., 1927, **41**, 177.
3. Dorst, S. E., and Wherry, W. B.: Ohio State Med. J., 1928, **24**, 539.
4. Hiss and Zinser: Textbook of Bacteriology, New York, D. Appleton & Co.
5. Morris, R. S., and Dorst, S. E.: AM. J. MED. SCI., 1929, **177**, 631.
6. Larson, W. P., and Eden, H.: J. Am. Med. Assn., 1926, **86**, 1000.

A CLINICAL STUDY OF GUMMA OF THE LIVER.*

BY JULIUS FRIEDENWALD, M.D.,

PROFESSOR OF GASTROENTEROLOGY,

AND

THEODORE H. MORRISON, M.D.,

ASSOCIATE PROFESSOR OF GASTROENTEROLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF MARYLAND, BALTIMORE, MD.

(From the Gastro-Enterological Clinic of the Department of Medicine, University of Maryland.)

SYPHILIS of the liver is a rather uncommon disease. It occurs, according to Brunsting,¹ in approximately one patient out of every 2000 admitted to the Mayo Clinic. Hale White² notes that among 8500 autopsies performed at Guy's Hospital from 1885 to 1904, there

* Read at the Meeting of the Association of American Physicians, Atlantic City, May 6, 1930.

were 23 with gummas of the liver and 72 with syphilitic cicatrices. Rolleston³ observes that among 11,300 autopsies at Middlesex Hospital between 1854 and 1900 gummas of the liver were noted in 40 instances. Of 5088 necropsies held at the Philadelphia Hospital, Flexner⁴ found 23 instances with gummas and 28 with cicatrices. Inasmuch as the diagnosis of hepatic syphilis can ordinarily only be definitely established upon the general evidence of syphilis in connection with the history, Wassermann test and antiluetic treatment followed by long periods of clinical observation, it is our object to present here only our cases of gumma of the liver. This type is one form of hepatic involvement of this disease, in which the evidence is usually sufficiently definite to warrant a positive diagnosis from clinical signs alone. We have selected therefore but 10 instances of this affection from a fairly large series of cases of hepatic syphilis, which we consider have fulfilled all the necessary criteria as the basis of this paper.

The following histories present in abstract the most important findings in our cases:

Case Histories. CASE I.—E. H., male, aged thirty-nine years, presented himself for treatment because of a large mass in the region of the liver, which he himself had first detected. He had not experienced pain, but had had considerable abdominal distention, and had lost 10 pounds in weight, during the past three months. He had entered a hospital for observation and treatment. The diagnosis of an abdominal tumor was made and an exploratory operation advised. The patient was unwilling to undergo this procedure and presented himself for further examination at our Clinic. His previous history was unimportant. He had been in good general health until three months ago; and had at no time previously been affected with abdominal distention or indigestion in any form. No alcoholic history could be elicited nor any of a former ascites. The patient however, presented a definite statement regarding a chill associated with fever extending over a period of three days during the early part of his present illness, which was, apparently overcome by the administration of quinin. He was unable to furnish any history of a primary lesion or present any information of a secondary stage.

On physical examination the patient was found to be a man of good build, but with an evident loss of considerable flesh. There was no evidence of jaundice or cachexia. The heart and lungs were normal. The blood pressure was 135 systolic, 80 diastolic. The abdomen was somewhat distended, the liver extending 3 inches below the costal arch, the left lobe also being somewhat enlarged. The surface of the liver was hard and there was considerable tenderness on moderate pressure. A large nodular rounded mass was easily palpable to the right of the epigastrium projecting upward apparently under the costal arch. Movable dullness could easily be detected indicating the presence of considerable free abdominal fluid. The spleen was somewhat enlarged, the edge extending two fingers breadth below the left costal arch. There was no fever and the blood picture showed a slight anemia. Red blood corpuscles 4,130,000; hemoglobin 72 per cent. The Wassermann test was +++. The gastric secretion following an Ewald test breakfast showed a total acidity of 64, free hydrochloric acid, 48; the urine and stools were normal. The diagnosis of gumma of the liver was made and the patient placed upon an intensive antisyphilitic treat-

ment (mercury and iodids) and within six weeks the mass and tenderness of the liver as well as ascites had entirely disappeared. A marked reduction in the size of the liver was also noted, although the Wassermann reaction still remained positive even after a year.

CASE II.—C. B., male, aged forty-six years complained of indigestion with abdominal pain for a period of two years. His past history revealed the ordinary diseases of childhood and in addition a venereal sore on the genital organs three and a half years ago, which continued on a few weeks and then disappeared. There was no alcoholic history. During the past two years the patient has been complaining greatly of indigestion in the form of fullness, distention and nausea following meals; but not of vomiting. For the past year abdominal pain has been rather severe and a mass was observed in the upper right abdomen, which has gradually enlarged. The patient has lost 23 pounds in weight during the past six months and though his appetite has remained good, he has been afraid to eat.

Physical examination revealed a rather slender, weak individual of 130 pounds with evident loss of flesh. A slight icteric tint was noted in the conjunctivæ. His thoracic organs were normal. The blood pressure was 110 systolic, 70 diastolic. The liver was markedly enlarged extending three fingers' breadth below the costal arch and the left lobe was also slightly palpable; on pressure there was marked tenderness but no evident muscle spasm. Two distinct nodular masses were palpable in the right lobe of the liver; the one about the size of an orange just above the lower border, and the other that of an egg beneath the costal arch; both were situated near the center of the lobe and were definitely attached to the liver. The spleen was not palpable; there was no movable dullness or other evidence of ascites. The temperature was usually normal, though occasionally a rise to 99.5° was observed. The blood examination revealed a hemoglobin of 58 per cent, red cells, 3,900,000; differential count, normal. The Wassermann reaction was + + + +. A liver functional test (Rosenthal's tetrachlorophthalein) showed moderate retention 13 per cent in fifteen minutes and 10 per cent in an hour. The stool was normal; urine normal with the exception of a trace of bile. The gastric contents was normal; total acidity, 54; free hydrochloric acid, 42, following an Ewald test breakfast. The gastrointestinal Roentgen ray series revealed no abnormalities.

From the history of a primary lesion together with the clinical findings and the positive Wassermann reaction, the diagnosis of gumma was evident. Under antiluetic treatment (mercury and iodids) the gummatous masses soon began to disappear and within six weeks were hardly any longer perceptible. The abdominal pain and indigestion also vanished rapidly and were no longer present following two weeks' treatment. The patient gained 30 pounds within six weeks.

CASE III.—J. K., male, aged thirty-seven years, had complained of acute attacks of pain occurring at irregular intervals in the upper right quadrant of the abdomen for a year. His past history was negative except for the prolonged use of alcohol. It was negative as to syphilis. The pain complained of was extremely violent at times and would often radiate around to the right shoulder blade. On two occasions the administration of morphia was required for relief. The attacks were never accompanied with chills or fever, though these occasionally occurred associated with indigestion which was almost constantly present during the past five months. The indigestion consisted of fullness, marked distention, nausea, vomiting of bile and extreme constipation. The patient had lost 35 pounds in weight.

On examination he presented a rather cachectic appearance with evident loss of weight. There was a distinct icteric tint in the conjunctivæ and the

cutaneous veins over the lower chest and abdomen were markedly enlarged. The lungs were normal; the heart slightly enlarged to the right, though no murmurs could be detected. The blood pressure was 168 systolic, 120 diastolic. The abdomen was somewhat distended, movable dullness was noted, indicating the presence of free fluid. The liver was distinctly enlarged three fingers' breadth below the costal arch and was tender on pressure, and the edge distinctly hard. The surface was filled with nodular masses varying in size from that of a marble to a lemon. The spleen was palpable two fingers' breadth below the costal arch. The inguinal glands were slightly enlarged.

The blood examination revealed a secondary anemia; red blood cells 3,100,000; hemoglobin, 53 per cent; the differential count was normal. The Wassermann test was +++. A marked functional disturbance of the liver was present as was revealed by the bromsulphalein test. The total acidity of the gastric contents was 36, free hydrochloric acid, 0. The urine had a specific gravity of 1012, and contained a heavy trace of albumin, but no sugar and showed a distinct icteric discoloration. The stool was normal. A gastrointestinal Roentgen ray series revealed no abnormalities except the stomach and duodenum pulled over and held in the right upper quadrant region.

It was difficult at first to determine whether we were dealing with cirrhosis, carcinoma or syphilis (gumma) of the liver. The treatment however, definitely pointed to the correct diagnosis of gumma.

Following a vigorous antisyphilitic treatment (mercury and iodids) many of the nodules, rapidly disappeared, and the pain, indigestion and distention diminished markedly within two weeks. The nodules in the liver were gradually reduced in size and the patient gained 25 pounds within six weeks. Although some enlargement of the liver, together with small nodules, could still be detected following a year's treatment as well as a recurrence of the indigestion when the patient was indiscrete in his diet, his general appearance and a gain in weight of 40 pounds were definite evidences of the correctness of the diagnosis. It is probable that the small nodules still remaining in the liver were the cicatrices occurring as the result of the disappearance of the gummas.

CASE IV.—F. M., male, aged forty-nine years, complained of abdominal pain at times as well as indigestion for a period of over three years. He had previously enjoyed good health, and with the exception of occasional attacks of indigestion had had no other disturbances. He denied syphilitic and other infections, and had never been addicted to the use of alcohol. There was but slight loss of flesh. The pain was moderate, and was located in the epigastrium and in the right upper quadrant. With this, there was considerable gastric distress, nausea, occasional vomiting and a few attacks of chills and slight rise of temperature.

On examination, jaundice of the skin and scleræ of a moderate degree was noted. The heart and lungs were normal; blood pressure 140 systolic, 80 diastolic. The abdomen was soft. The liver was enlarged three fingers' breadth below the costal arch and was tender on pressure. There was no enlargement of the left lobe. The spleen was not palpable. A rounded mass, the size of an egg was noted in the epigastrium which was definitely associated with the liver. The blood picture was normal, red blood cells, 4,900,000; hemoglobin, 85 per cent; blood Wassermann reaction, +++. The gastric contents were normal; total acidity, 56 and free hydrochloric acid, 34. The urine contained a heavy ring of bile but was otherwise normal. The stools were alcoholic. A gastrointestinal Roentgen ray series revealed no abnormalities.

The diagnosis of gumma of the liver was made which was confirmed by

the therapeutic test. Following thorough antiluetic measures, the ieterus, indigestion and mass promptly disappeared and following a year's treatment there was no further evidence left of the former affection.

CASE V.—S. F., male, aged forty-one years, complained of abdominal pain, indigestion and loss of flesh for more than a year. He gave a definite history of a primary syphilitic lesion with secondary manifestations dating back eight years. Inasmuch as he was forced to travel almost constantly his treatment was much interrupted and was finally discontinued. His past history was unimportant except for overindulgence in alcohol extending over many years. He has had discomfort and pain though not intense under his right costal arch which had become almost constant. In addition there was fullness in the abdomen and distention following meals as well as constipation. He had never been affected with chills, rise of temperature or jaundice, but had lost 15 pounds in weight. Shooting pains and numbness in his legs were experienced at times.

On examination the pupils reacted normally and were equal; there was no evidence of ieterus. The thoracic organs were normal. Blood pressure 120 systolic, 80 diastolic. The abdomen was soft. There was no evidence of free fluid in the abdomen. The liver was enlarged reaching a hand's breadth below the costal arch. It was tender on pressure, the edge being firm and hard. There was also a slight enlargement of the left lobe. The spleen was not palpable. There were two distinct masses in the liver, the size of hazelnuts; one in the epigastrium just below the ensiform cartilage; the other below the costal arch in the mammillary line. There were numerous other small masses throughout the surface of the liver. The inguinal glands were enlarged and firm. The knee reflexes were somewhat sluggish, but there was no definite evidence of involvement of the central nervous system.

The blood picture was normal; red cells, 5,100,000; hemoglobin, 80 per cent; blood Wassermann, ++++. The gastric secretion showed a true achylia. The liver functional test (bromsulphalein) was normal; and the urine and stool likewise showed no abnormalities. A gastrointestinal Roentgen ray series presented no evidence of any lesion in the gastrointestinal tract. Following an intensive treatment with mercury and iodids, the masses almost melted away, and the gastric symptoms likewise disappeared so that in the course of three months there remained no further signs of these conditions except for a moderate enlargement of the liver and a continued positive blood Wassermann reaction.

CASE VI.—O. M., male, aged forty-four years, complained of abdominal pain, distention and loss of flesh. His past history was unimportant, except that he had the usual diseases of childhood and also a syphilitic infection twenty-years ago. He had a primary lesion followed by a secondary eruption and underwent treatment for a short time. He suffered no further disturbance until the onset of his present illness.

About eight months ago, he began with indigestion in the form of discomfort under the right costal arch and more recently with pain in addition to fullness, distention, nausea and occasional vomiting. On two occasions he vomited slight amounts of bloody material and occasionally noted black stools. He had lost 20 pounds in weight.

The patient presented the appearance of a rather emaciated individual almost cachectic in appearance; there was an icteric tint to the skin and conjunctivæ. The cutaneous veins in the lower chest and upper abdomen were somewhat enlarged. His chest organs were normal. Blood pressure, 168 systolic, 75 diastolic.

The abdomen was much distended; the liver markedly enlarged reaching nearly a hand's breadth below the costal arch. The left lobe was also quite

TABLE I.—IMPORTANT FINDINGS IN TEN CASES OF GUMMA OF THE LIVER.

Number	1	2	3	4	5	6	7	8	9	10
Name	E. H. M.	C. B. M.	J. K. M.	F. M. M.	S. F. M.	O. M. M.	J. R. M.	J. H. M.	K. T. M.	R. B. D. M.
Sex	♂	♂	♂	♂	♂	♂	♂	♂	♂	♂
Age	39	46	37	49	41	44	35	49	36	32
History of primary infection	○	+	○	○	+	+	○	○	○	+
Time between appearance of primary lesion and invasion of liver	3½ yrs.	8 yrs.	20 yrs.	4 yrs.
Abdominal disorders and pain	○	+	+	+	+	+	+	+	+	○
Indigestion, nausea, vomiting, eructation, distention, hēmatemesis	+	+	+	+	+	+	+	+	+	○
Chills and fever	+	○	+	+	○	○	+	+	○	○
Jaundice	○	+	+	+	○	+	+	+	+	○
Gummatous masses	+	+	+	+	+	+	+	+	+	+
Enlargement of liver:										
Right lobe	+	+	+	+	+	+	+	+	+	+
Left lobe	+	+	+	+	+	+	+	+	+	+
Enlargement of spleen	+	○	+	○	○	+	+	○	○	○
Loss of weight in pounds	10	23	35	0	15	20	25	0	15	20
Dilatation of cutaneous veins	○	○	+	○	○	+	○	○	○	○
Ascites	+	+	+	+	+	+	+	+	+	+
Blood Wassermann test	+	+	+	+	+	+	+	+	+	+
Gastric secretion:										
Total acidity	64	54	36	56	32	30	22	56	76	66
Free HCl	48	42	0	34	0	10	0	42	63	50

enlarged. Both lobes were extremely tender on pressure, and were filled with nodules varying in size from that of a pea to an orange. There was definite movable dullness in the abdomen indicating the presence of free fluid. The spleen was enlarged, reaching three fingers' breadth below the costal arch. The biceps and knee kicks were hyperactive. Babinski and Oppenheim normal. The blood picture showed 3,480,000 red cells. Hemoglobin, 60 per cent; differential count, normal; blood Wassermann, + + +. The gastric analysis revealed a total acidity of 30; free hydrochloric acid 10, following an Ewald test meal. The urine was normal with the exception of containing a trace of bile. The bromsulphalein liver functional test showed a retention of 45 per cent for five minutes and 15 per cent for thirty minutes. It was difficult at first to determine whether we were actually dealing with cirrhosis or with syphilis of the liver. The therapeutic test however, definitely cleared up the diagnosis. In four weeks following antiluetic treatment (mercury and iodids) the free abdominal fluid disappeared following a single tapping; the liver became markedly reduced in size; the small masses disappeared entirely and the large ones greatly diminished. The spleen was no longer palpable. Following another examination made after six months, no further evidence of the liver affection could be detected. The patient had gained 35 pounds in weight.

CASE VII.—J. R., male, aged thirty-five years, complained of indigestion for a period of four and a half years, during which he had lost 25 pounds in weight. During this time, there had been considerable pressure, fullness, flatulency and pain under the right costal arch. The pain was never severe, but extremely distressing. Nausea and vomiting were frequent.

His past history was unimportant. He denied having had lues. On examination he presented the appearance of a seriously ill individual, who had lost considerable flesh. His skin and sclerae showed a moderate jaundice. The heart and lungs were normal; blood pressure 164 systolic, 85 diastolic. His abdomen was somewhat distended and tympanitic. There was no evidence of the presence of free abdominal fluid. The liver was enlarged, extending three fingers' breadth below the costal arch and was tender on pressure, especially along the course of its lower border, which was firm and hard. Just above the lower edge about its center a mass was detected which was hard and firm, the size of an egg, which projected high up from the liver surface, and could be easily outlined. The left lobe of the liver was somewhat enlarged, but the spleen was not palpable. The inguinal glands were slightly enlarged on both sides and tender. The blood picture showed 3,200,000 red cells; and 52 per cent hemoglobin. The blood Wassermann was + + + +. The bromsulphalein liver functional test showed a slight retention. The urine contained a heavy trace of bile, but was otherwise normal. The gastric contents showed an achylia; total acidity, 22, free hydrochloric acid, 0. A gastrointestinal Roentgen ray series revealed nothing abnormal except a few right upper quadrant adhesions. The diagnosis of malignancy was considered but the positive Wassermann reaction pointed rather otherwise. A vigorous antiluetic treatment was instituted with most beneficial effect. The mass in the liver gradually disappeared, the liver itself became much reduced in size and the pain and digestive symptoms likewise abated. The patient gained 15 pounds in weight and appeared perfectly well following seven months' treatment.

CASE VIII.—J. H., male, aged forty-nine years, complained of abdominal discomfort and pain for a period of three months. He had always previously enjoyed good health and had never been affected with indigestion. A history either of a primary syphilitic lesion or of alcoholism could not be obtained. The abdominal discomfort occurred in the form of attacks of pain

in the right upper quadrant, some of which were quite intense. None of these attacks were accompanied with chills or fever. The patient had had eight or nine of these attacks and in but one was morphia required for relief; between the attacks, he was quite well, and suffered no indigestion. He has not lost any flesh.

On examination, the patient's appearance was that of an individual enjoying good health. His heart and lungs were normal. Blood pressure 120 systolic, 80 diastolic. His abdomen was soft, the liver was enlarged just a finger's breadth below the costal arch; the edge being firm and tender. A hard mass, the size of a hazelnut could easily be palpated just to the right of the epigastrium beneath the costal arch, which was definitely associated with the liver. The spleen was not enlarged. The blood examination revealed a normal blood picture. The blood Wassermann, however, was + + + +. The urine and stool were normal. A gastric analysis showed a total acidity of 56, free hydrochloric acid, 42, following an Ewald test breakfast. The bromsulphalein functional liver test was normal. A gastrointestinal Roentgen ray series revealed no abnormalities. A cholecystogram showed that the gall bladder emptied normally, and there was no evidence of stones. A probable diagnosis of gumma of the liver was made and antiluetic treatment instituted. The mass as well as the pains rapidly disappeared and had entirely vanished within six weeks.

CASE IX.—K. T., male, aged thirty-six years, complained of indigestion and pain in his abdomen. His past history was unimportant and he denied the presence of any syphilitic infection. About six months ago, he began with indigestion associated with symptoms of acidity; pain and discomfort in his stomach appearing several hours after meals, which were relieved by food and by alkalis. The pains gradually became more intense. He lost 15 pounds in weight.

On examination, the patient presented the appearance of a rather healthy individual. His heart and lungs were normal. Blood pressure 125 systolic, 80 diastolic. His abdomen was soft and relaxed; the liver was enlarged one finger's breadth below the costal arch. There was a distinct mass in the epigastrium slightly to the right of the median line and just beneath the costal arch the size of a lemon. The spleen was not palpable. There was a distinct tender area in the epigastrium and the edge of the liver was also tender on pressure.

The blood examination revealed perfectly normal conditions except for a + + + Wassermann reaction. The gastric secretion showed a hyperacidity; total acidity, 76; free hydrochloric acid, 63. The urine and stools were normal. A gastrointestinal Roentgen ray series revealed nothing further than a spastic pylorus and adhesions in the upper and lower right abdominal quadrants. The urine and stool were normal.

The history suggested peptic ulcer, but the mass in the liver, the positive Wassermann test, and the absence of Roentgen ray evidence rather pointed more definitely to gumma of the liver. The therapeutic test fully confirmed the latter impression. After five weeks of thorough antiluetic treatment consisting of mercury and iodids the mass and digestive symptoms entirely disappeared, however, the Wassermann reaction continued positive.

CASE X.—R. B. D., male, aged thirty-two years complained of loss of weight, stomach trouble and a mass in his abdomen. His past history revealed the usual diseases of childhood and a venereal sore on the genitals four years ago, which remained for two weeks, and then disappeared. An appendectomy was performed two years ago. His present illness dates back one and a half years with fullness and gas in his stomach occurring several hours following meals, which was much relieved by eructations. There was

no pain, nausea or vomiting. About three weeks ago he first noted pain and a mass in his abdomen just beneath the right costal arch, which began to increase in size and extended toward the midline. He lost 20 pounds in weight within a year. His appetite remained good, his bowels regular, and stools normal. On physical examination he presented the appearance of a well-built individual; there was no evidence of loss of flesh. His heart and lungs were normal. The abdomen was soft, and just below the costal margin on the right side near the midline was felt a firm nodular tender mass, well-defined, the size of an orange which was definitely attached to the liver and moved with respiration. There was no muscle spasm present. The spleen was not palpable. The genitalia and extremities were negative. Reflexes, hyperactive biceps and knee kicks. Babinski negative as well as Oppenheim and Gordon; negative ankle clonus. There was at first an intermittent daily temperature to 100° to 100.6° F.

The blood picture showed 3,780,000 red cells and 55 per cent hemoglobin, but was otherwise normal. The blood Wassermann was negative, the Kahn however, was + + + +. The urine was negative with the exception of containing a slight trace of albumin. The stool was normal. A gastric analysis following an Ewald test breakfast showed a total acidity of 66; free hydrochloric acid, 50. A liver functional bromsulphalein test was negative. A gastrointestinal Roentgen ray series revealed no defects; there was present, however, a spastic and irritable pylorus. The diagnosis of gumma of the liver was made, and the patient given iodids and finally mercury. The temperature fell to normal within nine days, and with this, the mass gradually diminished in size and almost disappeared.

Discussion. **ETIOLOGY.** Tertiary syphilis of the liver may be divided into two types; the congenital and the acquired forms. In the hundred cases of McCrae and Caven⁵ five were of the congenital type.

Sex. Males are more susceptible to hepatic syphilis than females. According to Rolleston,³ Tresawana noted 100 males to 41 females and McCrae⁵ 66 males to 34 females. All of our cases of gumma of the liver occurred in males.

Age. The incidence of this affection is greatest, according to Rolleston, between the twenty-fifth and fiftieth years. The acquired cases in McCrae's series occurred between the thirtieth and fiftieth years. The ages of ours ranged between the thirty-second and forty-ninth years.

History of Syphilis. While in the congenital type, there is usually a definite history of syphilis present, this is not always observed in the acquired forms. A definite history of a primary infection occurred in 37 per cent of McCrae's cases; it was present in 4 of our 10 cases (40 per cent). The time that elapsed between appearance of the primary lesion and the syphilitic invasion of the liver varied in McCrae's cases from eighteen months to twenty-five years; in ours from three and a half to twenty years. According to Rolleston, affections of the liver produced by alcohol, malaria or even former jaundice predispose to this disease by lowering the resistance of this organ. While the abuse of alcohol apparently increases the liability to syphilis of the liver, it should not be inferred

that gumma of the liver necessarily follows upon alcoholic cirrhosis inluetics.

PATHOLOGIC ANATOMY. Tertiary syphilis of the liver occurs as a diffuse cirrhosis or as a gummatous affection; the latter being of the small miliary or of the large nodular type. The nodular form not infrequently involves the left lobe as well as the right, a sign, according to McCrae, of importance in the diagnosis. A perihepatitis has also been described, in which the lesion appears as whitish or greyish linear or stellate scars occurring in the outer surface of the liver. The scars may be minute or relatively large, averaging in size from that of a small pea to several inches in diameter or length. They may extend a few millimeters downward to the liver parenchyma.

Relation of Clinical Manifestations to the Pathologic Condition. It has been generally maintained that in tertiary syphilis the clinical manifestations are rare in comparison to the frequency of the disease. Gumma of the liver occurs often in a latent type and is not discovered until at autopsy. Mauriac⁶ found that of 7497 cases of tertiary syphilis, hepatic symptoms occurred only in 41 instances.

The factors especially involved in the production of symptoms are due, according to Rolleston, to the size, extent and location of the lesion in the liver.

A large gumma will produce the usual signs of a tumor and by irritating and distending the capsule of the liver causing perihepatitis will occasion pain. A small gumma located in the surface of the liver may not produce symptoms, but when located in the portal fissure may cause jaundice or ascites. Toxic symptoms in either instance, as anemia, fever and general weakness may be due to absorption of toxic products.

SYMPTOMATOLOGY. Many cases without doubt escape recognition, others not infrequently remain undetermined until late in the course of the disease when therapeutic measures are no longer encouraging. Before localizing hepatic symptoms are noted, general manifestations in the form of digestive symptoms, loss of weight, fever, jaundice and ascites are frequently observed. Occasionally, however, the tumor itself may first be accidentally detected before other clinical signs are revealed. McCrae observed previous ascites in 10 of his cases, all of which required tapping, the ascites having occurred from some months to eleven years prior to the onset of the present illness.

The onset of this affection is usually gradual, the most prominent signs being pain and abdominal distention. Then symptoms of indigestion manifest themselves in the form of abdominal discomfort, nausea, and vomiting, which are often associated with chills and fever. There is also noted, a marked loss of weight and not infrequently a mild form of jaundice and dilatation of the abdominal surface veins. The liver gradually enlarges and may finally extend to or below the umbilicus and ascites is not infrequent. The most

important sign of the disease, is, however, the detection of the gummatous mass in the liver. The spleen is frequently enlarged.

Pain. Inasmuch as gummata extend to the surface, the pain is produced by a perihepatitis or by the stretching of the capsule of the liver. It may entirely localize itself in the right hypochondrium or radiate to the back or right shoulder. The pain may be intense and occur in attacks or may be more moderate but constant; often only producing a fullness in the region of the liver. Pain occurred in 9 of our 10 cases; in 2 of which there were acute attacks simulating gall-stone colic. Abdominal distention is most frequently produced by ascites but may be in some instances the result of pressure from an enlarged liver. It occurred in 6 of our cases; in 3 due to pressure of abdominal fluid.

Indigestion. Disturbances of the digestion are not uncommon and frequently occur long before definite signs of the disease are detected, though with the progress of this affection they become aggravated. Indigestion occurred in 9 of our 10 cases from three months to four and a half years before the diagnosis was established. The most important of these symptoms are nausea and vomiting; though eructations, gaseous distention and acidity also occur and occasionally hematemesis has been observed. Nausea occurred in 5 of our cases and nausea with vomiting in 4 instances; vomiting of blood with melena in one; discomfort from gas in 4; hyperacidity in one.

Chills and Fever. Fever is said to occur more commonly without chills due probably in most instances to perihepatitis or softening of a gumma. The rise in temperature may be of short or long duration and may continue on steadily for weeks; being moderate in most instances, but may rise to 103° F. or over at times. Fever occurred in 18 per cent of Stokes cases, and in 3 of our cases in all with chills. It is striking how quickly the temperature disappears under antiluetic treatment; which not uncommonly occurs within a few days.

Loss of Flesh. This is a very common symptom and a most important feature of the disease. It occurred in 8 of our cases varying between 10 and 35 pounds with an average of 20 pounds of loss in weight.

Jaundice. This may occur either to a slight or intense degree. It is frequently mild and may be periodic, at times, of the obstructive, at others, of the nonobstructive type. Jaundice occurred in 5 of our cases; in one to a marked extent.

Dilatation of the Cutaneous Veins. This has often been noted. It occurred in 2 of our cases.

Enlargement of the Liver. The enlargement of the liver is an important feature of this disease, and is observed in all instances. This develops gradually with the progress of the disease, but may occur rapidly. Though the enlargement may be marked, reaching

8 to 10 cm. below the costal arch, in some instances, the edge of the liver may not extend more than 2 to 3 cm. beyond this area.

McCrae has called attention also to the frequent enlargement of the left lobe of the liver in this disease as an important aid in the diagnosis. This occurred in 5 of our cases. The border and surface of the liver is usually firm, hard and tender on pressure. The pain produced on palpation, may be intense but is usually moderate. Tenderness of the liver was present in 9 of our 10 cases.

Ascites. Ascites occurs not uncommonly. It is present according to Stokes⁷ in about a third of the cases, and may be transient due to a localized peritonitis or perihepatitis. Its rapid disappearance usually under antiluetic treatment without tapping often, is a noteworthy feature of this disease. Ascites occurred in 3 of our cases, and tapping was performed but once.

Gumma. The most important evidence of hepatic syphilis is the presence of a gummatous mass. This is found either in the form of nodules or a large rounded tumor. The gumma not only involves the right lobe, but not uncommonly the left lobe as well. McCrae attaches much importance in diagnosis to this finding. In 89 of his cases in which tumorous masses were present, the left lobe was involved in 49. The nodules are most frequently found in the epigastrium, and somewhat to the right under the costal arch. This occurred in 6 of our cases; in 2 others there were many irregular masses extending almost over the entire surface of the liver, and in 2 very distinctly separate irregular masses were noted.

The Spleen. Enlargement of the spleen is frequently observed. This organ was palpable in 50 per cent of McCrae's cases and was hard and firm in all. It was enlarged in 3 cases of our series, reaching as far as 4 cm. below the costal arch in one instance.

The Blood. A moderate secondary anemia is not uncommon. This occurred in 5 of our cases. The differential count was normal in all instances. The Wassermann test is most important in diagnosis; but is not always positive. It was negative in 8 of McCrae's 41 cases. When found negative, recourse should be made to the Kahn test and if doubt still exists, a provocative test should be undertaken. A Wassermann test should always be performed with ascitic fluid, whenever this can be obtained, which may aid in clearing up the diagnosis.

The Gastric Secretion. Test meals were given in all of our cases. The gastric acidity was normal in 5 instances; hyperacidity occurred in 3 and achylia in 2.

The liver functional test (bromsulphalein). This test is usually positive in those instances in which there is extensive involvement of the liver, but becomes negative when the disease subsides under treatment. It was positive in 4 of our cases.

DIAGNOSIS. The diagnosis is not usually difficult, provided a clear history of a luetic infection can be obtained in a patient presenting a mass in the liver with enlargement of this organ. If in addition, discomfort or pain in the right upper quadrant of the abdomen and abdominal distention, indigestion, fever, loss of flesh, jaundice, ascites and enlargement of the spleen are present, then the diagnosis is more certain. It is strengthened by means of a positive Wassermann test. But at times many of these signs and symptoms may be absent thereby rendering the diagnosis uncertain.

The two diseases with which gumma may be especially confused are carcinoma and cirrhosis of the liver. If the possibility of lues be held in mind, whenever a mass of doubtful origin is present in the liver, the diagnosis need not be attended with great difficulty. Whenever doubt still remains, the result of the therapeutic test will usually clear up the diagnosis. Greater difficulty may also arise at times in the differential diagnosis between gumma and portal cirrhosis especially when an alcoholic history is present. In these instances careful palpation should be undertaken following withdrawal of the ascitic fluid, but here too, the therapeutic test may become necessary before a definite diagnosis can be made.

PROGNOSIS. The prognosis of gumma of the liver is ordinarily satisfactory, if the treatment is carried out thoroughly and undertaken sufficiently early before resulting cirrhosis has developed. The effect is striking in these cases not only clinically, but recovery can also be demonstrated often by means of the liver functional tests. Notwithstanding the satisfactory clinical results, the persistence of the positive Wassermann reaction in the blood in tertiary syphilis of the liver is well recognized, and it is frequently impossible to reverse this reaction even in spite of extremely intensive therapeutic measures.

TREATMENT. The treatment to be instituted in gumma of the liver is the administration of iodids and mercury. The effect as has already been stated is extremely favorable as the results in all of our 10 cases indicate. The masses and ascites disappear and the liver and spleen diminish rapidly in size. Our experience is entirely in accord with that of McCrae⁵ as well as of Brunsting,¹ that the administration of arsphenamin or other arsenic preparations in these cases is dangerous and their use is therefore contraindicated.

Summary. Gumma of the liver is a rather uncommon disease. Males are far more susceptible than females, the incidence being greatest between the thirtieth and fiftieth years. A definite history of a primary infection is obtained only in about 40 per cent of the cases. The time elapsing between the appearance of the primary lesion and the hepatic disease varied in our cases from three and a half to twenty years. Previous affections of the liver render the liver more susceptible to this affection. The clinical manifestations

are rare in comparison to the frequency of this affection. Gumma of the liver is often latent. The factors involved in the production of symptoms are especially related to the size extent and location of the lesion.

Before localizing symptoms occur, general manifestations such as digestive symptoms, loss of flesh, fever, jaundice and ascites are frequently observed. The onset is usually gradual; the most important signs being pain and abdominal distention. Symptoms of indigestion are often associated with chills and fever, and progressive loss of weight, and not infrequently jaundice. The liver gradually enlarges, and ascites is not uncommon. The most important sign is, however, the detection of a gummatous mass in the liver which may occur as nodules or as a large rounded tumor which may involve the left as well as the right lobe of the liver. Enlargement of the spleen is frequent. The blood Wassermann test is not always positive. Diagnosis is not difficult if a definite history of luetic infection can be obtained in a patient affected with a mass in the liver, who has discomfort and pain in the right upper quadrant of the abdomen with distention, indigestion, fever, loss of weight, jaundice, ascites and enlargement of the spleen. It is strengthened by a positive Wassermann test. The two diseases with which gumma of the liver may be especially confused are carcinoma and cirrhosis. In case of doubt, the result of the therapeutic test will clear up the diagnosis.

The prognosis is satisfactory if treatment is thoroughly carried out and undertaken sufficiently early before a resulting cirrhosis has developed. The results are striking. In spite of this however, the persistence of the positive Wassermann reaction in the blood is well recognized.

The treatment consists in the administration of iodids and mercury. The effect of these remedies is extremely favorable. The masses, ascites, and other symptoms disappear, and the liver and spleen rapidly diminish in size. The administration of arsphenamin is dangerous and its use is contraindicated.

REFERENCES.

1. Brunsting: Proceedings of the Staff Meetings of the Mayo Clinics, 1929, 4, 124.
2. White, Hale: Common Affections of the Liver, James Nisbet & Co., 1908, p. 192.
3. Rolleston and McNee: Diseases of the Liver, Gall Bladder and Bile Ducts, Macmillan & Co., 1929, p. 392.
4. Flexner: New York Med. J., 1902, 75, 101.
5. McCrae and Caven: AM. J. MED. SCI., 1926, 172, 781.
6. Mauriac: Gas. hebdom. de méd., Paris 2, 1888, S 25, 564.
7. Stokes: Modern Clinical Syphilography, W. B. Saunders Company, 1927, p. 777.

RENAL GLYCOSURIA, WITH KETOSIS DURING SURGICAL COMPLICATIONS.*

By FRANK N. ALLAN, M.D.,

ASSOCIATE IN SECTION IN DIVISION OF MEDICINE, THE MAYO CLINIC; INSTRUCTOR OF MEDICINE, THE MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH, GRADUATE SCHOOL, UNIVERSITY OF MINNESOTA,

AND

FRANCES R. VANZANT, M.D.,

FELLOW IN MEDICINE, THE MAYO FOUNDATION, ROCHESTER, MINN.

RENAL glycosuria was first described more than thirty years ago, but until modern methods of determination of the blood sugar came into general clinical use there was uncertainty regarding the nature of the disturbance. The characteristic feature is the excretion of sugar in the urine without abnormal elevation of the concentration of sugar in the blood. The cases reported here illustrate a phenomenon in such cases which has apparently received little attention.

Case Reports. CASE I.—A woman, aged thirty-three years, came to The Mayo Clinic in 1918 because of migraine and because of a tumor of the thyroid gland which caused symptoms of pressure. The urine contained a small amount of reducing substance, but further investigation of this condition was not made. A single adenoma was removed from the thyroid gland. Convalescence was satisfactory.

The patient returned to the Clinic in August, 1928, because of another tumor in the thyroid gland and because of a verrucous condition of both nipples. There was no evidence of hyperthyroidism, and the basal metabolic rate was normal. The urine contained 1.08 per cent sugar, representing 5.55 gm. in a twelve-hour specimen. The results of a tolerance test in which 100 gm. of glucose were administered are shown in Table I.

TABLE I.—GLUCOSE-TOLERANCE TEST: 100 GRAMS GLUCOSE. Case I.

Time.	Blood sugar, mg. for each 100 cc.	Volume, cc.	Urine.	
			Sugar.	
			Per cent.	Total, gm.
Fasting	103	125	0	0
One-half hour after glucose . . .	164	150	0	Trace
Two hours after glucose	132	300	0.87	2.6
Three hours after glucose	118	175	1.77	3.1

September 1, 1928, subtotal thyroidectomy was done for multiple adenomas, and both nipples were excised because of the possibility of a malignant condition. Examination of the urine on the day of the operation showed acetone bodies and a large amount of sugar, as judged by a qualitative test. Because the condition was not understood at the beginning, insulin was given in small doses for five days. Yet intense glycosuria con-

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tinued for several days. Symptoms of hypoglycemia did not appear. The determinations of blood sugar showed it to be normal.

The diet was limited to the equivalent of 120 gm. of glucose until the seventh day. The excretion of sugar had then decreased to traces. The allowance of carbohydrate was raised, but glycosuria disappeared. A trace of sugar was excreted when the diet contained the equivalent of 500 gm. of glucose. The fasting blood sugar was determined repeatedly but was never above normal (Table II).

TABLE II.—CLINICAL AND LABORATORY DATA. CASE I.

Date.	Blood sugar, mg. for each 100 cc.	Sugar excreted.		Diet, glucose equivalent, gm.	Comment.
		Per cent.	Total, gm.		
1918.					
April 22	Trace		
1928.					
Aug. 11 . . .	110	1.08	5.55	General	
Aug. 20 . . .	103	...	Trace		
Sept. 1	+	..	Thyroidectomy; 15 units insulin.
Sept. 2	+	..	25 units insulin.
Sept. 3 . . .	94	2.55	23.00	120	20 units insulin.
Sept. 4 . . .	100	3.76	24.40	120	10 units insulin.
Sept. 5 . . .	114-119	...	+	120	5 units insulin.
Sept. 6	0.62	10.80	120	
Sept. 7 . . .	110	0.11	2.20	200	
Sept. 8	0.25	2.60	200	
Sept. 9	0.05	0.82	200	
Sept. 10	0	300	
Sept. 12	0	400	
Sept. 13 . . .	100	0.18	1.60	500	

Comment. The excretion of sugar without abnormal elevation of the blood sugar both before and after operation points to the diagnosis of renal glycosuria. The blood-sugar curve following the administration of glucose differs from the response considered normal, in the slight elevation of the blood sugar present until the second and third hours. Yet the existence of glycosuria for ten years without influence on the patient's health indicates absence of any serious defect in the utilization of sugar. The intense glycosuria and ketonuria after operation contrasted with the slight glycosuria observed previously and subsequently.

CASE II.—A woman, aged twenty-three years, came to The Mayo Clinic in September, 1929, because of recurring attacks of biliary colic. She said that she had diabetes. Three and a half years before, seven months after the birth of her second child, she consulted her physician because of a vaginal discharge and pruritus of the vulva. Examination of the urine showed the presence of sugar (6 per cent). There had been some increase in appetite and she was gaining in weight. A restricted diet was prescribed and 21 units of insulin were given daily. Hypoglycemic symptoms occurred frequently. The appetite became abnormally great, and the diet was not followed closely. The body weight increased to more than 200 pounds.

A third pregnancy had terminated successfully three months before the visit to the Clinic. During the pregnancy hypoglycemic symptoms had been so frequent that the dosage of insulin was reduced and it was finally discontinued. The patient continued dieting more or less, but did not take

insulin after the birth of this child. During the three and a half years of treatment frequent examination of the urine revealed glycosuria constantly with the exception of the test of a single specimen on one occasion. The blood sugar, as determined on a few occasions, had not been above normal. The appetite was poor during pregnancy and became worse when the attacks of biliary colic commenced during the puerperium. To this fact the patient attributed loss of weight amounting to approximately 50 pounds.

On examination at the Clinic the patient weighed 152 pounds. There was slight tenderness over the region of the gall bladder. Pelvic examination disclosed cystic cervicitis with moderate leukorrhea. Roentgen ray examination revealed a poorly functioning gall bladder containing stones. At the first test the urine contained 1.92 per cent of sugar, representing 10 gm. in a twelve-hour specimen. The fasting blood sugar was 80 mg. for each 100 cc. The urine did not contain albumin. The blood urea was 22 mg. for each 100 cc.

Parallel tests of the blood and urine were made September 4. At 11 A.M., three hours after a breakfast which contained the equivalent of 40 gm. of glucose, the urine gave a strongly positive test for sugar; the blood sugar was 100 mg. for each 100 cc. Ten units of insulin were given before the noon meal, which contained the same equivalent of glucose. At 4 P.M. the blood sugar was 75 mg. for each 100 cc., and a few minutes later slight hypoglycemic symptoms appeared. Urine excreted during the hour previous to the blood test showed a strong test for sugar. The results of a glucose-tolerance test made September 25 are shown in Table III.

TABLE III.—GLUCOSE-TOLERANCE TEST: 100 GRAMS GLUCOSE. CASE II.

Time.	Blood sugar, mg. for each 100 cc.	Volume, cc.	Urine.	
			Sugar.	
			Per cent.	Total, gm.
Fasting	90	60	0.93	0.58
One-half hour after glucose	143	140	1.12	1.70
Two hours after glucose	133	190	2.87	5.50
Three hours after glucose	110	100	2.81	2.80

Cholecystectomy and appendectomy were performed September 27, 1928. The pathologist reported chronic catarrhal cholecystitis with cholelithiasis and chronic catarrhal appendicitis.

On the day before the operation the amount of sugar excreted was 16.2 gm. Immediately after the operation the excretion increased tremendously although the intake of glucose was much less; on the day of the operation 63.5 gm. of sugar were excreted, yet the blood sugar was not elevated; at 11 A.M. it was 95 mg. for each 100 cc., and at 4 P.M. it was 100 mg. Glycosuria was accompanied by ketonuria for five days. Table IV shows how the excretion of sugar gradually decreased again until the thirteenth day after operation. At this time phlebitis of the left femoral vein appeared. The temperature rose to 102° F. and the patient suffered from considerable pain and malaise. Again the excretion of sugar increased to from three to four times that which had appeared before. Ketonuria was present at the beginning of the illness, but the administration of salicylates masked the later tests. When the fever and inflammation subsided the excretion of sugar diminished and was approximately the same when the diet contained the equivalent of 240 and of 120 gm. of glucose.

A report was received from the patient two months after she was dismissed from the hospital. She was in good health, and was living on a normal diet, avoiding only excessively sweet foods.

TABLE IV.—CLINICAL AND LABORATORY DATA. CASE II.

Date.	Per cent.	Total, gm.	Diet, glucose equivalent, gm.	Maximal temperature, °F.	Comment.
1929.					
Sept. 23 . .	1.25	12.5	120	Normal	
Sept. 24 . .	1.03	7.7	120	Normal	Insulin given, which caused reaction
Sept. 25 . .	0.50	8.0	180	Normal	Glucose-tolerance test
Sept. 26 . .	1.91	16.2	200	Normal	
Sept. 27 . .	5.29	63.5	100	99.8	Operation
Sept. 28 . .	5.23	57.5	35	99.4	
Sept. 29	100	99.6	Specimen of urine lost
Sept. 30	80	99.4	Specimen of urine lost
Oct. 1 . . .	4.13	35.1	120	Normal	
Oct. 2 . . .	3.95	31.6	120	Normal	
Oct. 3 . . .	3.23	20.2	..	Normal	
Oct. 4 . . .	3.70	26.0	..	99.4	
Oct. 5 . . .	3.47	24.3	..	Normal	
Oct. 6 . . .	3.89	37.0	240	99.8	
Oct. 7 . . .	4.69	37.5	240	100.2	
Oct. 8 . . .	2.93	33.7	..	99.2	
Oct. 9 . . .	5.59	22.4	..	102.0	Phlebitis
Oct. 10 . . .	6.93	72.7	200	102.0	
Oct. 11 . . .	7.07	65.4	..	102.0	
Oct. 12 . . .	7.43	89.2	..	102.2	
Oct. 14 . . .	6.71	70.3	..	101.0	
Oct. 15 . . .	6.57	78.9	..	101.0	
Oct. 16 . . .	6.89	68.9	..	99.6	
Oct. 17 . . .	4.87	40.2	..	Normal	
Oct. 18 . . .	4.27	51.2	..	99.2	
Oct. 19 . . .	2.45	23.3	..	Normal	
Oct. 20 . . .	2.25	14.6	240	Normal	
Oct. 21 . . .	0.99	12.9	..	Normal	
Oct. 22 . . .	0.91	8.6			
Oct. 23 . . .	0.79	7.5			
Oct. 24 . . .	0.64	6.4			
Oct. 25 . . .	0.43	5.4			
Oct. 26 . . .	0.52	4.8			
Oct. 27 . . .	0.31	3.1	120		
Oct. 28 . . .	0.55	3.7			
Oct. 29 . . .	0.81	8.3			
Oct. 30 . . .	0.51	5.2			
Oct. 31 . . .	0.23	2.8			

Comment. The patient had definite renal glycosuria. The condition had unfortunately been mistaken for diabetes mellitus, and needless dietary restriction and treatment with insulin had been carried on for more than three years. Treatment was, of course, ineffective in checking glycosuria. The increase in excretion of sugar and the appearance of ketonuria after the operation and again during the febrile illness were striking.

CASE III.—A woman, aged thirty-nine years, came to the Clinic February 11, 1929, complaining of attacks of severe epigastric pain radiating into the throat and down both arms. Diaphragmatic hernia was suspected and the diagnosis was confirmed by Roentgen ray examination. The first specimen of urine examined showed slight reduction of Benedict's solution, and a second specimen contained 1.38 per cent sugar.

The fasting blood sugar was 90 mg. for each 100 cc. The urine contained albumin graded 1 on the first test and graded 2 on the second test. A specimen by catheter did not contain blood cells or casts. The return of phenolsulphonaphthalein in the test of renal function was 50 per cent. The result of a glucose-tolerance test is shown in Table V.

TABLE V.—GLUCOSE-TOLERANCE TEST: 100 GRAMS GLUCOSE. CASE III

Time.	Blood sugar, mg. for each 100 cc.	Urine.		
		Volume, cc.	Sugar.	
			Per cent.	Total, gm.
Fasting	98	25	0	
One-half hour after glucose . . .	123	200	0	
Two hours after glucose	106	325	0.82	37
Three hours after glucose	66	260	Slight reduction.	

Operation for repair of the hernia was advised, but it was postponed for two months. At the pre-operative examination glycosuria was again noted; a twelve-hour specimen, April 19, contained 1.33 per cent sugar, representing 6.2 gm., and a similar specimen, April 20, contained 0.87 per cent sugar, representing 4.5 gm. A trace of albumin was present in each case.

As a preliminary procedure to the closure of the hernia, a portion of the left phrenic nerve was removed in the neck April 23. The diaphragm was closed by abdominal operation April 30. Immediately after the second operation the patient had pneumonia with empyema, and convalescence was slow. Resection of a rib for drainage of the thoracic cavity was performed May 14, 1929.

After the operation the urine contained a larger amount of sugar, Benedict's test showing complete reduction. On the third day acetone bodies appeared. Determinations of blood sugar, May 1 and May 2, were 147 and 109 mg. for each 100 cc., respectively. Because of the appearance of hyperglycemia at the beginning and because of ketosis, insulin was given in small doses, 5 units being used twice May 1, three times May 2 and three times May 4. Intense glycosuria and ketonuria continued. During the night of May 4 mild symptoms suggesting hypoglycemia were noticed. A determination of blood sugar made on the afternoon of May 5 was 57 mg. for each 100 cc.; the carbon dioxid combining power of the plasma was 54 volumes per cent. The patient was seriously ill with pneumonia, the temperature having been elevated between 101° and 103° F. since May 2. She had been able to take little nourishment by mouth; glucose solution was therefore administered intravenously.

There was only one occasion on which fasting hyperglycemia was found, namely, the morning after the operation when the blood sugar was 147 mg. for each 100 cc. Through an error the determination of blood sugar May 2 was reported as 159 mg.; the condition of the patient was misinterpreted, and the administration of insulin was continued until hypoglycemic symptoms appeared.

During the next week the patient was still critically ill, but she was able to take food each day. She continued to excrete from 1.19 to 3.35 per cent sugar in the urine, amounting to from 13.1 to 31.3 gm. in twenty-four hours. It was difficult to obtain complete collection of the urine because of the prostration of the patient. The blood sugar was normal at all later examinations. May 7, it was 97 mg. for each 100 cc. and May 12 it was 102 mg. for each 100 cc.

After May 11, the urine contained traces of sugar each day until June 3. From this time on, glycosuria was not found. The patient was given a

general diet, but her appetite was variable and, as a rule, light. After thoracotomy the condition of the thorax gradually cleared. The patient gained strength steadily and was dismissed June 20, 1929.

Comment. The patient had intermittent renal glycosuria, since the threshold was somewhat above the normal fasting level for blood sugar. The amount of sugar excreted under ordinary circumstances was small. After the operation the excretion of sugar was increased to a considerable degree and ketonuria occurred.

Discussion. The combination of ketonuria and glycosuria is not characteristic of diabetes mellitus. Ketonuria may occur, of course, in a normal person during starvation, and the tendency to ketosis is even greater in an individual with renal glycosuria. If the excretion of sugar continues when the intake of glucose has been stopped, or when it is reduced so that there is a negative glucose balance, a condition which one might describe as superstarvation is established. In cases of renal glycosuria with excretion of a large amount of sugar (50 gm. or more each day) severe acidosis may develop if the diet is restricted. The situation is comparable to the ketonuria and acidosis occurring in animals with the artificial renal glycosuria brought about by treatment with phloridzin.

Reference to the influence of complications on renal glycosuria are scarce. Goldbloom described a case in which a child had renal glycosuria with ketonuria following pharyngitis. The excretion of sugar amounted to 1 per cent at the beginning but gradually diminished and disappeared in a month. Taussig reported a case of renal glycosuria in which excretion of a large amount of sugar with ketonuria occurred after an automobile accident which resulted in fracture of the clavicle. Under ordinary circumstances glycosuria amounted to 2 gm. or less daily, but after the accident it increased to nearly 3 per cent. The excretion of sugar was also increased to 13 gm. when the patient was under nervous strain because of family troubles. The report of a case by Meyer contains information bearing on this problem. A man who had renal glycosuria and a duodenal ulcer excreted sugar, graded 1, and acetone, graded 1, in January, 1927. In October, 1927, when perforation of the ulcer occurred, the urine contained sugar, graded 4, and acetone, graded 2. Another report of interest in this connection was published by Bowcock and Greene. They described a case with renal glycosuria observed during and after pregnancy. The woman excreted from 20 to 40 gm. of glucose each day during pregnancy. In the puerperium the excretion became less than 4 gm. each day.

Summary. The cases of renal glycosuria here reported show clearly that increase in the excretion of sugar may occur during the presence of a complication such as surgical operation or infection. The excretion of sugar may become so great that ketosis may develop unless care is taken to provide for the ingestion of sufficient glucose to maintain the utilization of adequate balance. In this

behavior renal glycosuria imitates diabetes mellitus. The mechanism involved, however, is entirely different. In the former case there is apparently increased permeability of the kidneys, and in the latter increase in the defect in utilization of glucose appears to be the important factor.

BIBLIOGRAPHY.

1. Bowcock, H. M., and Greene, E. H.: Observations in a Case of Renal Glycosuria During and After Pregnancy, *J. Am. Med. Assn.*, 1928, **90**, 502.
2. Goldbloom, A.: Renal Glycosuria in an Infant Twenty Months of Age, *Canadian Med. Assn. J.*, 1924, **14**, 950.
3. Meyer, J.: Renal Glycosuria and Duodenal Ulcer, *Med. Clin. North America*, 1928, **12**, 233.
4. Taussig, A. E.: Renal Glycosuria With Ketonuria, *Med. Clin. North America*, 1927, **11**, 355.

ACUTE INTERSTITIAL PANCREATITIS IN TWO CASES OF DIABETIC COMA.

BY ALVIN G. FOORD, M.D.,

PATHOLOGIST, BUFFALO GENERAL HOSPITAL, AND ASSISTANT PROFESSOR OF PATHOLOGY,
UNIVERSITY OF BUFFALO SCHOOL OF MEDICINE,

AND

BYRON D. BOWEN, M.D.,

ASSISTANT ATTENDING PHYSICIAN, BUFFALO GENERAL HOSPITAL, AND ASSISTANT PROFESSOR OF MEDICINE, SCHOOL OF MEDICINE, UNIVERSITY OF BUFFALO,
BUFFALO, N. Y.

(From the Buffalo General Hospital.)

ACUTE interstitial pancreatitis occurring in patients dying of diabetes is an uncommon lesion according to studies made by recent observers. Warren,¹ studying Joslin's material, found no cases in his series of 26 cases varying from fifteen to sixty-nine years of age. One of his series of 9 children,² all of whom died in coma, showed a swollen red pancreas which showed some infiltration with polymorphonuclear leukocytes and lymphocytes in the periphery of the organ, with an associated hyperplasia of the adjacent lymph nodes. Wilder³ found no acute pancreatitis in 55 cases studied microscopically. Gibb and Logan⁴ report the largest series of necropsies in cases of diabetes in recent literature, 147 in all. In this number, 6 showed evidence of an acute inflammatory change in the pancreas: 2 chronic localized abscesses, 1 necrosis of the head with productive fibrosis, 2 hemorrhagic and leukocytic infiltration, and 1 a diffuse, edematous, acute interstitial pancreatitis. These authors suggest that acute infections in the pancreas may be the cause of chronic productive fibrosis so commonly seen in the pancreas of diabetic patients, and that these acute inflammations may account for the sudden onset of the diabetes in certain cases.

Warfield⁵ suggests that upper abdominal pain in prediabetic coma may be due to an acute pancreatitis rather than to the coma *per se*, as usually taught. He found 7 cases in the literature and described 4 of his own cases of diabetes following acute pancreatitis. In 1 fatal case at operation, a hemorrhagic, swollen pancreas with fat necrosis was found. In a second case, necrosis with hemorrhage in the pancreas, most marked in the tail, was found at autopsy. In discussing Warfield's paper, Allen⁶ states that he was able to produce diabetes in animals by an acute pancreatitis which did not immediately destroy the islands or lead to fibrosis of the organ. He also states that he believes that further study will show that acute blood-borne pancreatic infections are the most common cause of diabetes, especially in the young. Joslin⁷ agrees with Warfield that in some cases of beginning diabetic coma, pain in the epigastrium may be due to an acute pancreatitis. He describes 1 case of a well controlled diabetic patient, aged forty-three years, who suddenly developed coma with abdominal pain, nausea and vomiting. With insulin the patient first improved and later gradually failed and died in coma three days after the onset. At necropsy a gangrenous pancreatitis with fat necrosis in the peritoneum was found. Rodriguez⁸ describes 1 case of sudden diabetic coma occurring in a patient with acute suppurative and necrotizing pancreatitis, associated with abdominal fat necrosis.

The 2 cases here reported occurred in young adults, both of whom showed a sudden onset of diabetic coma and death within twenty-four and thirty-six hours, respectively. In both the most important pathologic finding postmortem was an acute interstitial pancreatitis. No other infective process was demonstrated to explain the rapid death.

Case Reports. CASE I.—An unmarried man, aged twenty-three years, was first seen in January, 1926, when he was admitted to the hospital in a state of diabetic coma. He had acquired gonorrheal urethritis about three weeks prior to admission and he had had diabetic symptoms for about a month. His blood sugar was 832 mg. per 100 cc. and the CO₂ capacity of the plasma was 8.7 volumes per cent. He responded satisfactorily to treatment and was discharged two weeks later on a diet of 60 gm. of carbohydrate, 60 gm. of protein and 150 gm. of fat. His insulin dosage was 45 units daily. He came into the outpatient clinic regularly for a time but it was found that he did not adhere to his diet, so the insulin dosage had to be increased to 55 units daily. In August, 1927, he was again admitted in pre-coma. The blood sugar was 326 mg. and the CO₂ capacity of the plasma was 30.5 volumes per cent. In two weeks he was discharged on 50 units of insulin daily. He was not seen again until he was admitted in deep coma on December 10, 1929. He had omitted his insulin for twenty-four hours because of cramplike pains in his abdomen and inability to eat. He became drowsy four hours before admission but had been up and around the house prior to that. Upon admission his condition seemed critical. He was considerably cyanosed and his extremities were cold. His respirations were rapid and shallow and there were many crackling râles heard over both lungs. His pulse rate was 120,

rectal temperature 98.6° F. and his blood pressure, as near as it could be estimated, was 56 systolic and 30 diastolic. The blood sugar was 908 mg. and the CO₂ capacity of the plasma was 8.7 volumes per cent. The blood contained 25,000 leukocytes per c.mm. He received 150 units of insulin within a short period, salt solution subcutaneously, sodium bicarbonate solution per rectum and subcutaneous injections of caffein sodium benzoate and digitan. His condition showed no improvement and he died eight hours after admission.

Necropsy Findings Seven and a Half Hours After Death. The principal positive findings of interest were: The body was well nourished and there was no anemia. The lungs were boggy and deep purple in the dependent portions, and dripped considerable blood and some frothy fluid on section. No areas of consolidation were found. The heart was negative except for marked dilatation of the right side. The abdominal aorta showed a few yellowish streaks and patches. The liver was markedly enlarged (weight 4000 gm.) and yellow in color. Surfaces made by section were diffusely yellow and greasy, especially at the centers of the lobules. The spleen and kidneys showed a marked purplish congestion. The stomach and intestines showed nothing of interest, except marked cyanosis. The mesenteric and peripancreatic lymph nodes were enlarged up to 1 cm. in diameter, soft and diffusely yellow. The pancreas weighed 55 gm., was slightly reddened, and its capsule was tense. On section a few grayish flecks and streaks as well as some slight fibrosis were seen. The prostate, epididymis and urethra were negative. All the organs smelled strongly of acetone. The bladder urine showed glucose, 4+, acetone, 4+, and diacetic acid, 3+. The blood, especially from the liver, was heavily laden with fat, the serum appearing definitely milky.

Microscopic Findings. The pancreas in all portions of sections from head and tail showed foci of acute inflammatory exudate in the edematous perilobular stroma, consisting chiefly of polymorphonuclear leukocytes with occasional large mononuclear cells, with varying amounts of detritus, and in some places small foci of liquefied pools of pus were seen. Some of the ducts showed pus in their lumina. Adjoining many of the areas of acute inflammatory changes, and limited to these regions, necrosis of the acinar tissue without cellular infiltrate was noted. The specific localization of these necrotic areas about the places that showed acute inflammation and the fact that the remaining glandular tissue stained normally, was considered evidence of antemortem rather than postmortem change. A moderate interlobular fibrosis was seen in all parts of the organ. The islands of Langerhans were markedly reduced in number in the head, only 6 being found in three sections, 2 by 3½ cm. In the tail there was a moderate decrease. Those remaining showed no fibrosis, hyalinization, lymphocytic infiltration or hydropic degeneration. On a whole the cells showed somewhat scanty cytoplasm, deeply staining nuclei and in some islands were arranged in single strands more than usual.

The liver showed extreme fatty metamorphosis with huge vacuoles of neutral fat which stained red with Sudan III, in all of the cells of the centers and midzones of the lobules, and medium to fine similar staining droplets in the more peripheral cells. All the visible cytoplasm in the hepatic cells appeared coarsely granular or foamy. Sections stained for glycogen by Best's carmine method showed all the liver cell cytoplasm to be loaded with glycogen and glycogenic degeneration was present in many of the nuclei of the peripheral cells. Doubly refractive lipid needle-like structures which disappeared on heating were demonstrated in most of the cells which showed small to medium-sized fat droplets.

Sections of the kidneys showed moderate albuminous degeneration with necrosis of some of the cells of the convoluted tubules. Fine reddish droplets



FIG. 1.—Low power. Pancreas. Acute inflammatory exudate in interstitial tissue about bloodvessel. Case I.



FIG. 2.—High power. Pus in branch of pancreatic duct, and acute inflammatory exudate in surrounding tissue. Case I.

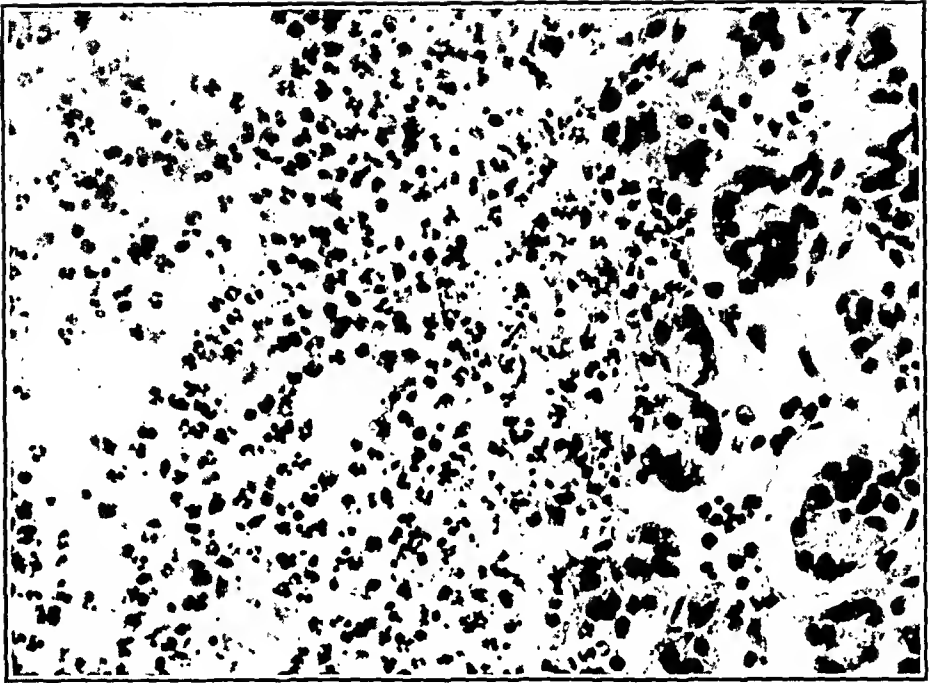


FIG. 3.—Medium power. Suppurative inflammation in interstitial tissue of pancreas. Case II.



FIG. 4.—High power. Small pocket of pus in interstitial tissue of pancreas. Case II.

of fat were found in most of the convoluted tubules in Sudan III preparations. Best's carmine stain revealed glycogen in large amounts in the cytoplasm and also in some of the nuclei of the loops of Henle.

Sections through both bases of the lungs showed marked hyperemia and some edema, but no evidence of inflammatory changes in the bronchi, alveoli or pleura.

A few of the fibers of the heart showed the presence of glycogen granules.

The spleen showed the findings of an acute splenic tumor and focal necrosis in some of the Malpighian bodies. Sudan III preparations showed large numbers of the large mononuclear cells of the pulp and germinal centers to be stained diffusely yellowish-red, but no globules of fat were seen. No doubly refractive substances were seen in fresh frozen sections.

The mesenteric and peripancreatic lymph nodes showed a most marked globular fatty infiltration, chiefly extracellular, as well as in the large free endothelial cells of the sinuses, especially the peripheral. Some fat deposit was seen in the walls of the small blood capillaries throughout the nodes. The fat stained deep red by Sudan III. Only an occasional doubly refractive crystal was seen.

The prostate and epididymis were negative.

Final Pathologic Diagnosis. Acute interstitial pancreatitis; diabetes mellitus; lipemia, glycosuria and acetonuria; hypostatic hyperemia and edema of lungs; dilatation of the heart; acute generalized passive hyperemia; extreme fatty metamorphosis of the liver; lipid in the kidney, abdominal lymph nodes, spleen; glycogenic infiltration of the liver, kidney and heart.

CASE II (We are permitted to report this case through the courtesy of Dr. J. Emerson Dailey).—A married woman, aged eighteen years, was admitted in unarousable coma. She was first seen in October, 1928. It appeared from a scant history obtained from the husband that she had had thirst for about two weeks prior to admission but had been active until vomiting occurred, eight hours before, after which she rapidly became unconscious. She was seven and a half months pregnant. Physical examination showed extreme dehydration and hyperpnea. Eighteen hours after the inception of acute symptoms her blood sugar was 1200 mg. per 100 cc. and the urine obtained by catheterization showed 7.5 per cent glucose. The leukocyte count was 18,200 per c.mm. Treatment with insulin subcutaneously and intravenously, salt solution subcutaneously and sodium bicarbonate solution per rectum, and caffein sodium benzoate produced no change in her condition and she died about twenty-four hours after the vomiting started.

Necropsy Findings. The necropsy was done by Dr. Dailey and the tissues were studied by Dr. William F. Jacobs and one of us (A. G. F.). Briefly the gross findings were not striking. The head and neck were essentially negative. There was slight dilatation of the right side of the heart. The lungs showed considerable hypostatic hyperemia and edema but no areas of consolidation. The pleural and peritoneal cavities were free from excess fluid. The liver showed moderate cyanosis as did the kidneys, adrenals and the gastrointestinal tract. The gall bladder and ducts were negative. The spleen was moderately enlarged, soft, red in color, and on section its parenchyma was soft and reddish-gray in color. The Malpighian bodies were obscured. The pancreas was normal in size and somewhat reddened and swollen. It showed a few small grayish streaks and spots throughout its extent. The pelves, ureters and bladder were negative. The uterus showed a seven-month normal pregnancy. All of the tissues had a strong odor of acetone.

Microscopic Findings. Sections through the tail of the pancreas showed a marked diffuse acute interstitial inflammation, characterized by the presence of various sized small abscesses and patches of polymorphonuclear leukocyte infiltration, hyperemia and edema in the interstices of the interlobular stroma. The larger abscesses, those about 1 mm. in diameter, had destroyed the neighboring acinar tissue, but the remaining glandular tissue was free from inflammatory infiltration. Pus was seen in many of the ducts. In the head and midportions the changes were much less extensive, but pus and desquamated epithelium were seen in the large branches of the pancreatic duct. In all sections the capsular connective tissue showed moderate edema and cellular infiltrate. The acinar tissue showed nothing of interest. The islands of Langerhans were very definitely decreased in number throughout. Of those remaining a few were much larger than the average normal. Otherwise they showed no noteworthy changes.

The other organs showed nothing of interest that was not noted grossly. The lungs showed a marked congestion and some edema but no pneumonia. Parenchymatous degeneration was seen in the liver and kidneys, and the findings of an acute splenic tumor were found in the spleen. There was no evidence of a disturbance of lipid metabolism.

Discussion. In one of the cases here reported, treatment was instituted early in the coma phase, while in the other it was late. We had clinical contact with Case I only; when he was seen a few hours after he had been able to walk to the bathroom, he was totally unconscious and had pulmonary edema, hypotonia and acrocyanosis indicating high-grade circulatory failure. Both patients had leukocytosis which is the rule in diabetic coma even though there is no clinical evidence of infection. In fact it has been our experience, Bowen and Hekimian,⁹ that coma cases with demonstrable infection do not regularly manifest leukocytosis.

Acute interstitial pancreatitis has not been demonstrated in our clinic in any necropsied cases of diabetic coma, and, as far as we can determine, there has been but one case that was in any way similar found in recent literature: A child, aged six years, reported by Warren, whose pancreas was swollen and red and showed a moderate infiltration of lymphocytes and polymorphonuclear leukocytes and hyperplasia of the regional lymph nodes. One case reported by Gibb and Logan, a man, aged sixty-two years, showed similar findings in the pancreas, but had in addition an infected hand. No mention was made whether or not this case died of coma.

It has been conjectured that the abdominal pain and leukocytosis which is so uniformly present in cases of diabetic coma are caused by acute pancreatitis. It would appear to us that if this were the case such lesions should be more commonly demonstrated and also it would seem that under such circumstances the pain should not abate so quickly and the leukocytes fall so rapidly after treatment. It is our belief that these two factors are in some way related to the acidosis. It is conceivable that lesser grades of acute pancreatitis, however, may be present as they might easily be overlooked unless the whole pancreas was sectioned.

Summary. Two fatal, fulminating cases of diabetic coma in young adults with necropsy findings have been reported. The chief pathologic finding in each of these cases was an acute diffuse interstitial pancreatitis which was probably a factor in the precipitation of coma.

Examination of the literature shows only one similar case (Warren) and another (Gibb and Logan) associated with an infected hand. In our 2 cases no source of the infection could be determined.

In one of our cases there was histologic evidence of a high degree of disturbance in lipid metabolism as manifested by a huge liver which showed extreme fatty metamorphosis, the deposit of lipid substance in the abdominal lymph nodes, spleen and kidney, and by lipemia. It is extremely probable that in this case, his diabetes had not been fully under control for some time as he had not previously seen a physician in about three years, and from past experience we knew him to be an unmanageable patient.

BIBLIOGRAPHY.

1. Warren, Shields, and Root, H. F.: Clinical and Pathologic Study of Twenty-six Cases of Diabetes, *Boston Med. and Surg. J.*, 1926, 194, 49.
2. Warren, Shields: Pathology of Diabetes in Children, *J. Am. Med. Assn.*, 1927, 88, 99.
3. Wilder, R. M.: Necropsy Findings in Diabetes, *South. Med. J.*, 1926, 19, 241.
4. Gibb, W. F., Jr., and Logan, V. W.: Diabetes Mellitus, a Study of One Hundred Forty-seven Autopsies, *Arch. Int. Med.*, 1929, 43, 376.
5. Warfield, L. M.: Acute Pancreatitis Followed by Diabetes, *J. Am. Med. Assn.*, 1927, 89, 654.
6. Allen, F. M.: Abstract of Discussion on Papers of Drs. Warfield and Lemann, *J. Am. Med. Assn.*, 1927, 89, 661.
7. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928, p. 390.
8. Rodriguez, J.: Acute Pancreatitis with Fat Necrosis, Complicated by Diabetic Coma, *J. Am. Med. Assn.*, 1924, 82, 203.
9. Bowen, B. D. and Hekimian, I.: Diabetic Coma: A Report of Eighty-one Cases, *Ann. Int. Med.*, 1930, 3, 1104.

THE ADRENALIN TEST AND CHOLESTEROL DETERMINATION IN THE DIAGNOSIS OF BORDERLINE HYPERTHYROIDISM.

BY J. WILLIAM HINTON, M.D., F.A.C.S.,

ASSISTANT PROFESSOR OF SURGERY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL; ASSISTANT ATTENDING SURGEON, BELLEVUE HOSPITAL; ASSISTANT ATTENDING SURGEON, ST. MARK'S HOSPITAL, NEW YORK CITY.

(From the Goiter Clinic of St. Mark's Hospital.)

PATIENTS frequently present symptoms of early hyperthyroidism with slight enlargement of the thyroid, and we are confronted with determining whether the goiter is the primary condition or whether there is some other condition which accounts for the symptoms, with the goiter merely an incidental finding. The adrenalin test, as advocated by Goetsch,¹ has been employed and, added to this,

TABLE I.—CLINICAL AND LABORATORY FINDINGS.

No.	Age.	Sex.	Duration.	Clinical diagnosis.	Basal metabolism.	Blood-pressure.		Pulse.		Notes of technician.	Treatment.	Follow-up
						Before.	After.	Before.	After.			
1	39	F.	6 months	Colloid	7/17/29 Plus 12	110/70	132/70 35 min.	80	104 35 min.	More quiet after test	Thyroid	Returns regularly; improving
2	48	F.	1 week	Adenoma, left; nontoxic	7/13/29 Plus 18	160/80	175/94 10 min.	102	112 25 min.	Quiet during test	Operation advised; refused	Does not return
3	25	F.	1½ years	Adenoma, right; nontoxic	8/17/29 Plus 6	120/70	142/70 5 min.	76	82 5 min.	Restless, pallor of lips and fingers after test	Operation advised; refused	Returns regularly; improving
4	16	F.	1 year	Colloid	9/11/29 Minus 19	120/60	126/60 5 min.	100	106 5 min.	Very quiet after test	Thyroid extract	Returns regularly; improving
5	30	F.	Thyroidectomy 8½ years ago; enlarged 3 yrs. after	Bosselated; non- toxic	10/16/29 Minus 1	100/70	118/60 5 min.	80	96 10 min.	Quiet after test	Operation	Returns regularly; symptom free
6	48	F.	9 years	Adenoma, right; nontoxic	10/30/29 Plus 13	154/99	140/96 15 min.	78	76 25 min.	Quiet after test	Operation	Returns regularly; symptom free
7	23	F.	3 weeks	Bosselated; non- toxic	1/23/30 Plus 5	120/70	144/68 10 min.	90	108 15 min.	Nervous, upset; would not give blood after test	Thyroid extract	Returns regularly; improving
8	23	F.	3 years	Colloid	1/15/30 Plus 7	120/70	140/80 5 min.	90	120 10 min.	Pale, then flushed	Thyroid extract	Returns regularly
9	14	F.	2 days	Bosselated; non- toxic	11/30/29 Minus 4	114/70	110/70	86	88 10 min.	Quiet after test	Thyroid extract	Returns regularly; not improved
10	45	F.	3 days	Adenoma, right; nontoxic	11/22/29 Plus 11	110/70	170/70 5 min.	80	80	Quiet after test	Operation advised; refused	Does not return
11	15	F.	1 year	Colloid	10/17/28 Minus 10 3/22/29 Plus 10	114/50	130/56 10 min.	92	100 5 min.	Slight tremor, felt dizzy; quiet after a few minutes	Thyroid extract	Returns regularly
12	24	M.	Insomnia since influenza 3 mos. ago; lost 10 pounds	Early exoph- thalmic	4/23/29 Plus 13	120/70	138/64 10 min.	80	90 10 min.	Quiet during test; no respiratory changes	Elixir luminal	Does not return
13	39	F.	3 years	Adenoma, right; nontoxic	4/25/29 Plus 19	120/80	120/80 5 min.	99	102 10 min.	Quiet, no tremor; palpitation after test	Operation advised; refused	Does not return
14	59	F.	10 years	Adenoma, mild toxicity	5/3/29 Plus 39	150/80	150/80	86	90 15 min.	Patient quiet and restful after test	Operation advised; refused	Does not return

15	42	F.	5 years	Colloid	1/7/29 Plus 10	100/56	128/62	80	100 5 min.	Very nervous after test	None	Does not return
16	31	F.	16 years	Bosselated; chronic hyper- thyroidism	6/27/29 Plus 18	154/82	166/88 10 min.	84	100 10 min.	Slightly nervous, face flushed; slight trem- or of lower limbs	Operation advised; refused; advised again Feb., 1930; refused	Returns irregularly
17	46	F.	6 years	Bosselated; non- toxic	6/10/29 Plus 10	110/78	190/74 15 min.	80	84 10 min.	Fairly quiet; refused blood	None	Does not return
18	48	M.	About 30 years	Adenoma, right and left; non- toxic	12/5/29 Minus 8	150/90	160/90 5 min.	84	104 5 min.	Restful, sleeping some of the time	Operation advised; refused	Returns irregularly
19	13	F.	Few weeks	Colloid	100/80	120/70 15 min.	84	92 10 min.	Slightly nervous; tremor after test,	Thyroid extract	Returns regularly; improving
20	28	F.	1 year after miscarriage	Exophthalmic	3/6/30 Plus 55	140/60	170/70 5 min.	140	150 5 min.	Restless; quiet after 15 minutes	Operation advised; considering same	In country for rest
21	16	F.	1 year	Colloid	1/29/30 Minus 5	120/70	130/80 10 min.	70	72 5 min.	Quiet after test; re- fused blood	Thyroid extract	Returns regularly; improving
22	31	F.	1 week	Colloid	2/19/30 Minus 9	120/88	130/60 15 min.	88	96 5 min.	Quiet during test	Thyroid extract	Returns regularly; improving
23	36	F.	5 years	Exophthalmic	5/4/25 Plus 98	144/70	145/58 5 min.	138	160 5 min.	Tremor before and during test	Refused operation for 4 years	Returns irregularly
24	19	F.	6 mos.; oper- ated in another hospital; never well after 3 Roentgen ray treatments	Recurrent ex- ophthalmic	7/10/29 Plus 40 5/1/29 Plus 51 5/22/29 Plus 37 9/20/29 Plus 20 11/20/29 Plus 32 6/12/29 Plus 27	140/80	160/80 5 min.	140	148 20 min.	Restless, talked all through test	Operation	Returns regularly; symptom free
25	42	F.	Enlargement since birth of child 24 years ago	Bosselated; strong toxiety	9/26/29 Plus 9	120/60	138/78	100	112 5 min.	Somewhat restless during test	Operation	Returns regularly; symptom free
26	15	F.	3 years	Colloid	9/26/29 Plus 9	120/76	138/90 5 min.	78	90 5 min.	Quiet during test	Thyroid extract	Returns regularly; improving

a white and differential count taken before the injection and at fifteen-, forty-five- and ninety-minute intervals after the injection. This addition Goetsch advocated in 1929 in a paper before the American Association for the Study of Goiter. In the positive cases of hyperthyroidism definite leukocytosis is produced after the injection. At the suggestion of Sweet,² we have added complete blood chemistry studies, with particular reference to the cholesterol findings in borderline and definite hyperthyroidism. He felt there might be a disturbance in the cholesterol metabolism. Tiber³ in a small group of cases of exophthalmic goiter found a definite decrease in the cholesterol. He felt the adenomatous goiters with hyperthyroidism would not show a disturbance in the cholesterol findings.

A special technician was employed for the work and the patients taken to the respiratory laboratory and allowed to rest for thirty minutes before taking their pulse and blood pressure or leukocyte count. After this the adrenalin injection was given as described by Goetsch:¹ "A hypodermic syringe armed with a fine needle which, when inserted, causes little discomfort, is then used to inject deep subcutaneously 0.5 cc. of the commercial 1 to 1000 solution of adrenalin chlorid into the deltoid region. I might say here, parenthetically, that the solution of adrenalin chlorid should be fresh as possible. . . . Readings of pulse, blood pressure and respirations and any changes in the subjective and objective manifestations are then noted every two and a half minutes for ten minutes, then every five minutes up to one hour and then every ten minutes for half an hour longer. At the end of one and a half hours the reaction has usually entirely passed off, sometimes earlier. . . . In a so-called positive reaction there is usually an early rise in systolic and a fall in diastolic blood pressures. In a very mild reaction the fall in diastolic pressure may occur alone. There is a rise in pulse rate of at least 10 and sometimes as much as 50 mm. or more of mercury. . . . In order to interpret a test as positive I have regarded it as necessary to have a majority of these signs and symptoms definitely brought out or increased. Thus there is at times a considerable exacerbation of the objective signs and symptoms, or there may be an increase of 10 points in the pulse and blood pressure together with a moderate increase of symptoms and signs; or, again, there may be only slight changes in pulse and blood pressure and considerable change in signs and symptoms. Any combination of this kind may be regarded as positive. . . . In this manner the diagnosis of the presence or absence of hyperthyroidism was placed on an impersonal pathologic basis, for very early hyperactivity could be recognized in the thyroid tissue even before there were any outspoken clinical symptoms produced."

Observations were made in 26 cases. The results are found in Tables I and II. There is included also a brief résumé of the clinical findings. The blood for chemical study was taken after the other studies were completed.



FIG. 1.—Clinical diagnosis, bosselated goiter, nontoxic. Adrenalin test positive.

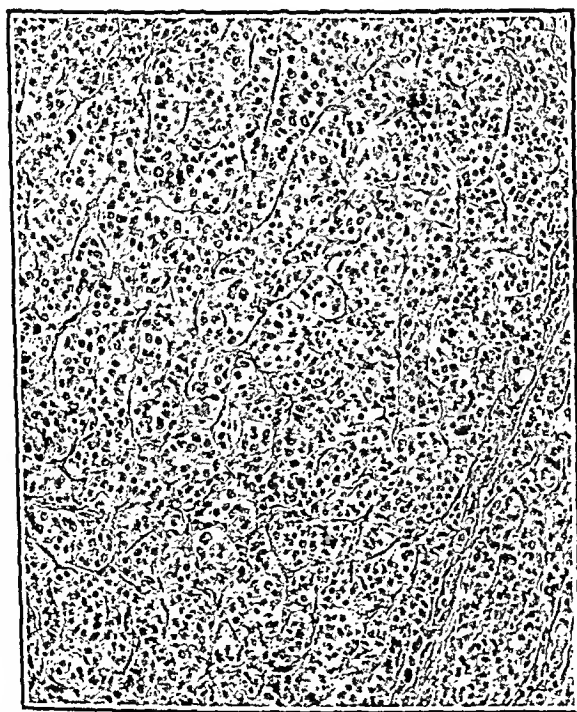


FIG. 2.—Clinical diagnosis, adenomatous goiter, nontoxic. Adrenalin test negative.

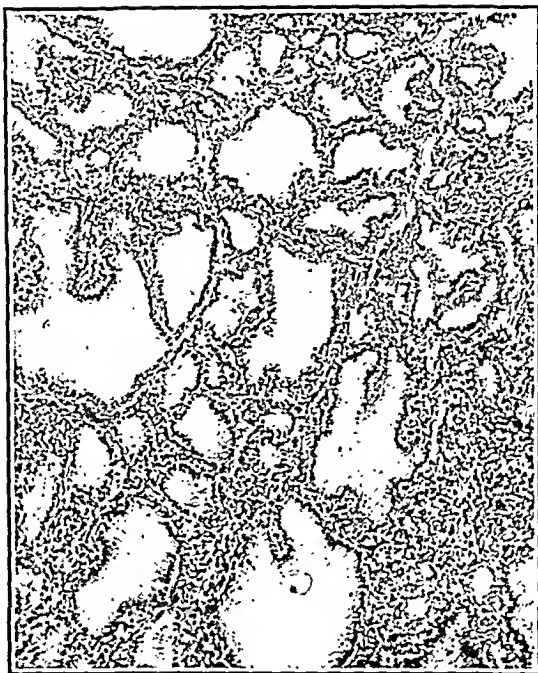


FIG. 3.—Clinical diagnosis, recurrent exophthalmic goiter. Adrenal test positive.



FIG. 4.—Clinical diagnosis, bosselated goiter with slight toxicity. Adrenalin test positive.

TABLE II.—LABORATORY FINDINGS.

Number.	Leukocytes.		Polys. (per cent).		Cholesterol.	Sugar.	Calcium.	Phosphorus.	Creatinin.	N.P.N.	Urea nitrogen.	Chlorids.	Uric acid.
	Before.	After 15 min.	Before.	After 15 min.									
1.	5,000	9,200	66	73	145	98.5	10.5	2.8	2.1	Q.N.S.	14	470	
2.	Would not allow blood to be taken.												
3.	7,200	10,500	65	80	135	130	13.5	2	2.9	35	16.35	500	
4.	5,600	8,000	56	70	182	120	12	1.8	1.5	29	16.5	250	
5.	6,000	12,600	59	81	180	111	12.	2.9	1.7	29.5	19.5	575	
6.	7,000	8,000	67	70	173	130	12	2.8	1.4	Q.N.S.	18	480	
7.	Would not allow blood to be taken.												
8.	7,200	12,000	69	75	159	81	Q.N.S.	Q.N.S.	1.6	23	14.5	250	
9.	7,400	10,600	68	77	140	99	10	3.3	1.4	23	10.8	475	
10.	Would not allow blood to be taken.												
11.	6,600	13,800	60	74	145	88	10.5	2.8	2	26	16	450	
12.	6,675	8,775	54	62	152	90	9.8	2.4	2.4	28	15.2	485	
13.	8,000	15,000	64	76	150	80	10.5	3.1	2.1	31	Q.N.S.	460	
14.	7,400	13,200	69	86	167	133	Q.N.S.	3.1	1.4	27	16	375	
15.	7,000	8,000	70	78	189	84	9.4	3.2	1.4	13.7	540	2.3
16.	7,000	8,400	60	70	189	94	8.4	4.6	1.1	18.1	545	
17.	6,600	9,200	58	70	Would not allow blood to be taken.								
18.	6,700	6,700	65	67	168	99	10.3	2.3	1.4	31	Q.N.S.	660	
19.	5,000	13,400	52	74	139	92	10	2.7	2.1	27	Q.N.S.	465	
20.	10,000	14,900	70	78	155.7	78.5	9.9	3.1	2	17.5	9.3	475	
21.	8,400	6,000	69	66	Would not allow blood to be taken.								
22.	8,000	7,000	70	65	172	72	10.9	3.1	1.7	18.5	9.95	473	
23.	5,600	8,400	60	69	170	99.5	8.8	2.1	2.1	28	18	520	
24.	9,000	12,000	72	79	182	81	9.5	3	1.8	31	17	468	
25.	7,200	12,000	70	80	184	74	8.4	1.6	1.4	Q.N.S.	15.16	438	1.8
26.	10,000	7,400	80	72	159	105	10	3.1	1.28	Q.N.S.	26	390	

Discussion. After reviewing the results of these cases it would appear that positive readings are obtained in practically all cases in which the adrenalin test, white and differential count was used. We must consider the test positive even in Cases 21 and 22. It will be noted that the metabolism in these cases was -15 and -9 . There are several other cases which did not clinically show signs or symptoms of hyperthyroidism and their metabolic rate was within normal limits. These cases have given positive adrenalin tests, but are improving under medical care and are considered not to have hyperthyroidism. In Cases 20, 23 and 24, which have definite exophthalmic goiters, the reactions were not much more marked than in Cases 8, 11 and 19, which have colloid goiters that are under medical treatment and improving.

The cholesterol determinations have remained within normal limits in Cases 20, 23 and 24 with definite hyperthyroidism, and also in Cases 18 and 22 with hypothyroidism. In none of the cases in this series was the cholesterol metabolism disturbed.

In Cases 5, 24 and 25 both the adrenalin test and the leukocyte count were positive for hyperthyroidism, while in Case 6 these tests were negative. The histologic pictures of these cases are quite different. Fig. 1 from Case 5 reveals the acini dilated and densely packed with colloid. The epithelial cells lining the acini are flat and interacinal and interlobular connective tissue is absent. Fig. 2 from Case 6 reveals solid masses of epithelial cells and practically no colloid is seen. Lobules cannot be distinguished and connective tissue is absent. Fig. 3 from Case 24 reveals the acini of varying sizes and enfolding of epithelial cells into the lumen of the acini with a moderate amount of colloid in the acini. Other areas reveal epithelial cells closely spaced and a slight amount of connective tissue. Fig. 4 from Case 25 reveals the acini of a relative uniform size and containing colloid and one area with a mass of undifferentiated cells.

From the above histologic findings one would expect quite a difference in the degree of reaction from the adrenalin test, but those cases interpreted as positive gave about the same degree of response.

Summary. As an aid in the diagnosis of borderline hyperthyroidism, the adrenalin test, with the leukocyte and differential count added, has not been of any assistance in making a diagnosis. The test seems to be so delicate that any patient with a thyroid enlargement will give a positive reaction unless a definite hypothyroidism is present. The cholesterol findings have not been reduced in this series of cases, regardless of the type of goiter.

BIBLIOGRAPHY.

1. Goetsch, Emil: Epinephrin Hypersensitiveness Test in the Diagnosis of Hyperthyroidism, *Penn. Med. J.*, 1920, 23, 431.
2. Sweet, Joshua E.: Personal communication.
3. Tiber, Arthur M.: Personal communication.

SOME PROBLEMS IN THE DIAGNOSIS AND TREATMENT
OF THYROTOXICOSIS.

BY FRED E. BALL, M.D.,

CHICAGO, ILL.

THYROTOXICOSIS presents many problems which at times cause great difficulty in diagnosis or treatment. My purpose is merely to present some that have been encountered and that have been followed for varying periods of time.

It has long been recognized that the basal metabolism is of great value in the diagnosis of thyrotoxicosis. This is especially true in the milder types of the disease. Miller and Raulston¹ have called attention to the group with only slightly elevated rates, and it is not uncommon to see cases where the diagnosis is only made after a basal metabolism has been taken. Several cases have been observed with typical symptoms of thyrotoxicosis, but with a normal rate. Later, however, the metabolism has become elevated, but without any change in the symptoms.

Case Reports. CASE I.—B. S., aged fourteen years. Previous to January 17, 1926, the parents had noticed that the patient was nervous, and she had been under a doctor's care for tachycardia. January 17 she came home from school because of blurring vision, became incoherent, had several convulsions, and developed a right-sided hemiplegia. The paralysis cleared up in twenty-four hours and she entered the hospital. It was at this time that the patient was first seen. The urine showed red blood corpuscles and many casts. The blood chemistry was normal. In ten days the urine had cleared up and only the tachycardia (140 to 150) remained. She had a marked tremor, moist palms and prominent eyes. No goiter was palpable. The basal rate was +5. The patient was taken home, but kept in bed. Because of the continued symptoms suggesting a thyrotoxicosis, a basal metabolism was taken at home in March. This was also +5. The tachycardia and tremor persisted, but the patient was allowed to get up. In May another metabolism was taken and this was +32. There had been absolutely no change in the symptoms. A small nodule was palpable in both lobes and the eyes seemed more prominent. Roentgen ray was started and in August the metabolism was +6. The Roentgen ray was then discontinued, but in December the rate was again +35. After more Roentgen ray the rate was +11 in September, 1927. The patient was last seen in April, 1928, with a rate of +14. She was put on one oridine tablet (10 mg. of iodine) twice a week.

Just what the infection was that caused the cerebral accident and the kidney irritation is not definitely known. However, the patient had been troubled with the tachycardia and nervousness earlier and these symptoms remained after all traces of the other difficulty had cleared up. It is indeed hard to explain why the two early metabolism tests were normal. Certainly the symptoms were the same with a reading of +32 as they were with a +5. No iodid, were prescribed at any time, nor was any treatment prescribed, except symptomatic, prior to the time the diagnosis of thyrotoxicosis was made.

CASE II.—W. E. S., aged fifty-nine years. The patient was first seen October 25, 1925, with a complaint of loss of 25 pounds in weight in two months with a good appetite. The pulse was 100 and there was a mild tremor. The examination was negative except for a blood pressure of 160 systolic and 80 diastolic. The urine was normal. The patient was leaving the city so a metabolism test was made at noon, although he had eaten breakfast. The rate was +12. Two weeks later another test was +20 and Roentgen ray was advised. December 12 the metabolism was +59 and on February 12 it was +9. The patient was last seen in August, 1926, and the metabolic rate was -10.

Because of the loss of weight with a good appetite, and in the absence of a diarrhea or sugar in the urine, the patient was considered to have a thyrotoxicosis before the metabolism test was made. A reading of +12 could be considered a little high, but the test was made under very unfavorable conditions and might easily be higher than the actual basal rate. However, the test two weeks later was +20 and subsequently +59. It is interesting to note that the symptoms had been present over a period of two months when the first metabolism test was taken.

CASE III.—M. N. L., aged forty-nine years. The patient was first seen in August, 1926. She was going through the menopause and was very nervous. There had been no loss of weight but she fatigued very easily. Her pulse was 104 and she had a very marked fine tremor. No goiter was palpable. Three metabolic tests were taken over a period of six weeks. Two tests were +4 and one -2. On September 17 the patient was put on Lugol's solution because the symptoms seemed typical of a thyrotoxicosis. December 7 another test was +35. The patient has not been seen since this time.

Because of previous experience, it was decided to put patients on small doses of iodids when they suggested a thyrotoxicosis clinically. The question naturally arises here whether the disease was induced by the iodids. This cannot be answered positively, but it is known that the patient presented the same symptoms with a rate of +35 as she did with the earlier rates of +4 and -2. The day Lugol's solution was started the pulse was recorded as 130. This may have been taken while the patient was nervous, but it does show the irritability of the heart. When the basal rate was +4, the pulse was recorded at 104 and when the metabolism was +35 the pulse was 96. The tremor and the nervous manifestations had not changed during the period of observation.

This group of cases naturally makes one a little more cautious about ruling out thyrotoxicosis with one metabolic test. I presume such cases are rather rare, but I do believe that occasionally patients are discharged with a diagnosis of neurasthenia or neurosis when they might possibly have fallen into this group. At the present time when the clinical diagnosis of thyrotoxicosis is not confirmed by metabolic tests, it is our custom to put patients on small doses of iodids as a therapeutic test. Oridine tablets (10 mg. of iodine) are now being used and are given once a day. Thompson² showed that the small doses of iodids are as effective as the large doses and this has been our experience.

Hypometabolism and Myxedema. Thompson³ has clearly pointed out that there is a group of postoperative cases which have a low metabolism, but which do not present the symptoms of myxedema. There is also such a group following Roentgen ray therapy.

CASE IV.—L. L., aged forty-five years. The patient was first seen in November, 1920. He presented the typical picture of thyrotoxicosis with hyperplastic goiter and exophthalmos. The basal metabolism was +48. The physical examination was essentially negative except for a fibrillating heart. Roentgen ray therapy was advised. January, 1921, the basal rate was +3, but the fibrillation still continued. April, 1922, the rate was +7 and the fibrillation was present. January, 1923, the rate was +5 and the heart was regular in rhythm. June, 1924, the metabolism was -12 with a regular rhythm. Since this time the metabolism has varied from -3 to -32, the last rate in July, 1929, being -23. He has presented no symptoms of myxedema except possibly some fatigue, which has not been troublesome.

This patient has had continuously a low basal rate for the past six years. It is interesting to note that this did not develop for two years after the last Roentgen ray treatment. It was believed he did not present the symptoms of myxedema, but because of the slight fatigue he was given thyroid extract. However, this symptom was not relieved. Basal rates were taken at frequent intervals while the patient was taking thyroid and when the metabolism approached a normal reading the heart began to fibrillate. The thyroid extract was discontinued and the heart returned to a normal rhythm. This fibrillation could be produced by giving more thyroid extract. The level at which this fibrillation occurred could not be determined exactly, but it was some place between -10 and 0. This observation seems of considerable interest in that the fibrillation could be produced with a low metabolism in a heart that had not fibrillated for three or four years. It has been three years since the fibrillation following thyroid extract therapy occurred and the patient has had no irregularity in that time.

In addition to the group with a hypometabolism, there is a group with true postoperative myxedema. Thyroid feeding will not always bring these cases back to normal function. Smith, Clute and Streider,⁴ from the Lahey Clinic, have reported a series of 100 consecutive cases of thyrotoxicosis operated upon at least one year previously. Of these, 92 per cent were cured, but 19 per cent had a basal rate below -10 and 15 had clinical symptoms of myxedema which could not be entirely relieved by thyroid extract. Fatigue and lack of endurance are the principal complaints, and these are severe enough so that they cannot carry on the occupations of normal individuals. Just what will be the outcome of these patients, time alone will tell. It is true they are relieved of the thyrotoxicosis, but they still have something which will not allow them to be normal.

CASE V.—L. W., aged twenty-six years. The patient was first seen in January, 1928. He developed a thyrotoxicosis in 1926 and was operated in September. The rate was +49 before operation and -6 following. In January, 1928, two tests were -11 and -12. His complaints were weakness, fatigue and lack of ambition. His wife said he was mentally sluggish and seemed uninterested. The pulse was 64 and the skin was fairly dry. The patient was put on thyroid and in February the rate was -5. It was -1 in March, but the patient was still very tired and not normal. He would work for two or three hours and then have to rest. He was then given 1 gr. of sodium iodid daily in addition to the thyroid. In October, 1928, the metabolism was -12. The patient was last seen in December, 1929. He had had no metabolism test and had stopped his medicine the last few

weeks as he had become discouraged because he did not feel well while taking it. He was again advised to take the thyroid, 4 gr. daily, and the iodids.

This is a typical case of the myxedema which cannot be relieved entirely by thyroid feeding. I am not sure the iodids improve the symptoms of this group, but this is being tried at the present time.

Hypometabolism and myxedema are two different things and should not be confused. Myxedema is a disease which should be diagnosed clinically and not by the metabolism test alone. As is illustrated here, the metabolism test may be brought to within normal limits and yet the patient may still present many of the original symptoms of myxedema. Hypometabolism, on the other hand, is diagnosed by the laboratory test. The basal rate is low, but the patient has no symptoms. In the case of hypometabolism auricular fibrillation was produced by bringing the basal metabolism within the range that is considered normal. It is assumed that this low metabolism is normal for that particular individual who has been subjected to destructive thyroid therapy.

Needless to say, many cases of postoperative myxedema can apparently be made to feel normal by thyroid feeding, but there is also this other group which remains distinctly myxedematous. Miller⁵ has raised the question of whether a less radical thyroid operation might be considered first, and then on the recurrent group use the radical surgical measures. This might possibly lower the percentage of myxedemas which cannot be brought back to normal by thyroid feeding. At least it would reduce very markedly the number of patients subjected to this danger.

Recurrent Thyrotoxicosis. The recurrent type of thyrotoxicosis with hyperplastic goiter is often a real problem to handle. There are a certain few of these which do not seem to respond to any type of treatment. Theoretically, if sufficient thyroid is removed the patient should be relieved of the thyrotoxicosis. Occasionally patients are seen where the thyroid tissue remaining after a subtotal thyroidectomy will rapidly hypertrophy with a return, or an increase, of the symptoms. When a second operation is performed there is again a hypertrophy of what seemed at operation an insignificant bit of tissue. There is also in this group a very occasional patient where after operation no thyroid tissue can be palpated and yet the symptoms persist or recur. Miller⁵ reports a patient seen by Phemister, when, after subtotal thyroidectomy, the basal rate remained +50. Several months later a second operation was performed to relieve the symptoms. Only two small pieces of thyroid tissue the size of a pea were found in the region of the lower poles. The bloodvessels to these bits of tissue were ligated and nothing was removed. The basal rate promptly returned to normal, and the patient returned to work for six weeks, after which the symptoms returned and the metabolism went up to +70. Phemister¹³ reports

that this case was later examined at autopsy and no thyroid tissue could be found. The only possibility is that there might have been some thyroid tissue in the base of the tongue. This was not examined histologically.

In this group of recurrent thyrotoxicosis Roentgen ray has not seemed to relieve the symptoms when surgery has failed and *vice versa*. It seems that either the disease must run its course or the patient must be given a myxedema, if that is possible.

CASE VI.—W. K., aged thirty years. The patient was first seen February 24, 1928. He had a typical thyrotoxicosis with hyperplastic goiter and exophthalmos. The metabolism was +79. A thyroidectomy was done March 9, 1928 and the right lobe, isthmus and left lobe (except a very small piece at the lower pole) were removed. He was discharged March 23, 1928, with a metabolism of +23, but was given 1 gr. of sodium iodid daily. He reëntered the hospital on April 14, 1928, with a rate of +65. The lower left pole of the thyroid had hypertrophied so that it was very easily palpated. Because of a severe sore throat he was not operated until June 1, 1928. A piece of thyroid the size of a golf ball was removed at that time. He was discharged June 12, 1928, with a metabolism of +29, but was given small doses of sodium iodid. He reëntered the hospital October 21, 1928, with a rate of +35. At this time Roentgen ray was advised.

June 29, 1929. The patient had had Roentgen ray for ten months and the metabolism was +29. There was a very small nodule palpable along the left side of the trachea. Roentgen ray was discontinued and he was put on 10 mg. of iodin (oridine) every other day.

August 30, 1929. The patient felt fine. The pulse was 72 and the rate 10. He had gained 10 pounds.

December 20, 1929. The patient had taken no iodin since August. He was nervous, had a slight tremor and the metabolism was +23. He was advised to take 10 mg of iodin, every other day.

In this case almost a complete thyroidectomy was performed, only a very small piece of the left lower pole remaining. The patient was discharged with a rate of +23 and was advised to take sodium iodid 1 gr. daily. In three weeks he was back in the hospital with a rate of +65 and a marked hypertrophy of the remaining thyroid. Many people have reported that iodin will not prevent a hyperplasia of thyroid postoperatively, but it is extremely interesting to note the rapidity with which it can occur. At the second operation the remaining thyroid tissue was removed, but even then the rate remained at a high level. Ten months of Roentgen ray could not reduce the metabolism and he has been on very small doses of iodin for many months. There is now a small piece of palpable thyroid on the left of the trachea, but further surgery has not been advised at this time.

CASE VII.—M. R., aged forty-four years. The patient was first seen in February, 1927, with a typical thyrotoxicosis with hyperplastic goiter and exophthalmos. The heart was fibrillating and there was a beginning cardiac decompensation. The metabolism was +72. He was put on iodids and operated April 4, 1927, with a rate of +30. The right lobe and part of the left lobe were removed. On discharge May 19, 1927, the metabolism was +35. The patient reëntered the hospital June 9, 1927, with a rate of +77. The remaining thyroid tissue was removed June 23, 1927. On discharge his metabolism was +32 and Roentgen ray was advised. He was given sodium iodid 1 gr. daily.

January 27, 1928. The metabolism was +46. He had had three complete series of Roentgen ray. There was a small nodule palpable in both lower lobes.

April 2, 1928. The metabolism was +16. The heart was still fibrillating. He was taking 1 gr. of sodium iodid twice a week. More Roentgen ray was advised.

March 8, 1929. He had had no Roentgen ray in eight months. The metabolism was +30. 10 mg. of oridine was advised daily.

March 21, 1929. The metabolism was +11, but the heart was still fibrillating and the patient had definite symptoms of thyrotoxicosis. There were nodules the size of walnuts in both lower lobes.

This is another example of the same type. Both surgery and Roentgen ray seem to fail and the remaining bits of thyroid tissue hypertrophy in spite of the patient's being on iodids. The metabolism is much lower and the patient is more comfortable on the small doses of iodids and eventually the disease may run its course as in the following case:

CASE VIII.—C. J., aged thirty years. The patient was first seen in September, 1924, with a typical thyrotoxicosis and hyperplastic goiter. The metabolism was +98. She was given Roentgen ray treatments from September, 1924, until April, 1925. The metabolism was +81 in June, 1925, and a thyroidectomy was performed. Both lobes, except small bits of tissue around the upper poles, and the isthmus were removed. In August, 1925, the metabolism was +60 and there was a nodule in both upper poles the size of a walnut. No iodine was given postoperatively.

October, 1926. The metabolism was +90. Lugol's solution, 3 minims three times a day, was advised.

November, 1926. The metabolism was +46.

May, 1927. The metabolism was +10. She had taken Lugol's solution since October, 1926. Oridine tablets (10 mg. of iodine) were advised twice a week.

November, 1927. The rate was +7. There were no symptoms of thyrotoxicosis, but in both upper lobes were nodules the size of a walnut.

June, 1929. No basal rate taken, but the patient was clinically normal.

Here again both Roentgen ray and surgery failed. It is true that only one operation was performed, but all the available thyroid tissue was removed at that time. Hyperplasia of the remaining bits about the upper poles occurred very rapidly. The patient was kept on small doses of iodids for a long period of time with the idea that it would at least lower the metabolism and make the patient more comfortable. In due time the disease subsided.

Thompson⁶ has reported the return to normal of a number of cases of thyrotoxicosis, following the continued use of small doses of iodids. In the past few years a number of such cases have been observed in this series, but I was inclined to look upon it merely as the termination of the disease. Possibly there is something more to this than has been suspected. Certainly such a thing shows promise and bears watching more closely.

I am sure everyone treating thyrotoxicosis sees these recurrent types occasionally. It is surprising to see the rapidity with which bits of thyroid tissue will hypertrophy even when the patient is taking iodids. In the cases reported both Roentgen ray and surgery were unable to control the disease entirely. It is true that the

patients were better after surgery, but the thyrotoxicosis could not be relieved entirely. The iodids seem to reduce the metabolism considerably, and the patients are much more comfortable. Eventually the disease may subside.

Phemister's case is certainly difficult to explain. In the absence of any demonstrable thyroid tissue at autopsy the patient had a marked thyrotoxicosis before death. Also the fact that at the second operation the patient developed a temporary normal basal metabolism as the result of ligating the bloodvessels to two small bits of thyroid tissue the size of a pea is something hard to understand.

Pregnancy and Thyrotoxicosis. The relationship of pregnancy to thyrotoxicosis is a problem which at the present time is not solved. Mussey, Plumer and Boothby⁷ report 42 (0.6 per cent) of 7228 women with thyrotoxicosis as being pregnant. They believe there is no evidence that the thyrotoxicosis was influenced by the pregnancy. Clute and Daniels⁸ found 0.41 per cent of 3678 women with thyrotoxicosis complicated by pregnancy. They also feel that pregnancy does not influence the toxicity of thyrotoxicosis and Hymen and Kessel⁹ are of the same opinion. Of 150 cases studied by Means and Richardson,¹⁰ 10 developed the thyrotoxicosis during pregnancy and 10 developed it after childbirth. Eberts, Fitzgerald and Silver¹¹ believe that 9 per cent of their 334 cases of exophthalmic goiter developed the first symptoms during pregnancy and 8 per cent more during lactation. Of 355 cases of toxic adenoma, they believe pregnancy was a predisposing cause in 14.3 per cent. These figures only tend to show the great difference of opinion. The following case history is of interest because of the repeated pregnancies which, from the history, seemed to cause symptoms suggesting a thyrotoxicosis. At least it is definite that the last pregnancy did, and the patient feels very sure the other reactions were similar.

CASE IX.—M. M., aged forty years. The patient was first seen June 17, 1929. She had had a swelling of the neck for fifteen years. When this was first noticed she had been given some pills (medication unknown) and these seemed to reduce the swelling slightly. With each menses the neck seemed to increase in size and decrease following the period. She had six children—the oldest aged seventeen years. After each pregnancy she became nervous, the neck would increase in size, and she would have to go to bed to rest. Two months ago, after her last child, she became nervous, developed a tachycardia and the neck became enlarged. She nursed the baby seven weeks, but was getting progressively worse so entered the hospital. She stated that during her pregnancy she always feels fine.

The patient had a bilateral nodular goiter, a fine tremor, tachycardia, wet palms, and a basal rate of +42. One oridine tablet was given daily and June 25, 1929, the metabolism was -12. She was operated upon June 28, 1929, and a subtotal thyroidectomy performed. No basal rate was taken before she left the hospital.

We cannot say, of course, that following each pregnancy this patient had a thyrotoxicosis, but we can say that she did following

the last pregnancy; the patient insists that this was no different than the previous reactions. Davis¹² reports 41 per cent of 520 consecutive patients reporting to him for pregnancy as having a visible hypertrophy of the thyroid. Eight of these patients returned to him within fourteen months with a thyrotoxicosis, and he says that by far the majority of his cases return to their own family physician.

CASE X.—C. A., aged thirty-six years. The patient was first seen in December, 1928. Four years previously she had had a thyrotoxicosis with a pregnancy. She was put in the hospital and given iodids. She does not know the basal metabolism and has had none since. She is now three months pregnant. In the last three months she has lost 15 pounds, has developed a tachycardia and tremor and is very nervous. She has had no iodids in four years. The basal rate was +29. She was given 1 gr. of sodium iodid daily. In April the rate was +24 and she was given 1 gr. of sodium iodid to take every other day. In June the metabolism was +43 and the pregnancy was terminated by Cesarean section. The patient did very well and the baby was apparently normal. Three weeks later the metabolism was +27, and she has not been seen since.

It is unfortunate that we do not have the metabolism during the first pregnancy or in the four years intervening. The patient states she felt quite well before the second pregnancy, and we can say that if there was a thyrotoxicosis present at the time of conception, it was greatly aggravated.

CASE XI.—H. N., aged forty-one years. The patient was first seen in March, 1929. She was two months pregnant. In the preceding few weeks she had developed a tachycardia, tremor and unusual nervousness. The thyroid was not palpable, but the metabolism was +31. A therapeutic abortion was advised and ten days later the metabolism was +2. In June, 1929, the basal rate was -5. Following her discharge from the hospital, the patient took 1 oridine table twice a week.

These case histories are rather misleading when one attempts to draw conclusions from them. First we have a patient who seemed to develop symptoms following childbirth; next a case where conception seemed to bring on a thyrotoxicosis, which was not relieved by childbirth; finally, a case where the thyrotoxicosis seemed to be initiated by conception and terminated by therapeutic abortion. Just what the relationship is between pregnancy and thyrotoxicosis is far from clear; but I do feel that there may be some. At least they are associated in enough cases to merit watching.

Summary. 1. Symptoms of thyrotoxicosis may be present preceding a rise in the basal metabolism, as illustrated here by 3 cases. Too much attention should not be given to one normal reading when the clinical picture suggests a thyrotoxicosis.

2. Hypometabolism and myxedema are two different things, and should not be confused. There is a group of cases which, following thyroidectomy, develop myxedema and which cannot be returned to normal by thyroid feeding.

3. Three cases of recurrent thyrotoxicosis with hyperplasia of

the remaining thyroid tissue are discussed. A recurrent thyrotoxicosis may exist where no thyroid tissue can be demonstrated.

4. Pregnancy and thyrotoxicosis are associated in a sufficient number of cases to bear careful study. The relationship between them, if any, is not at the present time clear.

NOTE.—Many of the cases presented in this paper are patients of Dr. Joseph L. Miller. I wish to express to him my appreciation for his courtesy in allowing me to present them and also for the great help and many suggestions he has given me.

REFERENCES.

1. Miller, J. L., and Raulston, B. O.: J. Am. Med. Assn., 1922, 79, 1509.
2. Thompson, W. O., *et al.*: Arch. Int. Med., 1930, 45, 261.
3. Thompson, W. O., and Thompson, P. K.: J. Clin. Inves., 1928, 5, 441.
4. Smith, L. W., Clute, H. M., and Streider, J. W.: Surg., Gynec. and Obst., 1928, 46, 323.
5. Miller, J. L.: AM. J. MED. SCI., 1929, 177, 98.
6. Thompson, W. O., Thompson, P. K., Brailey, A. G., and Cohen, A. C.: Arch. Int. Med., 1930, 45, 481.
7. Mussey, R. D.: Plummer, W. A., and Boothby, W. M.: J. Am. Med. Assn., 1926, 87, 1009.
8. Clute, H. M., and Daniels, D. H.: AM. J. MED. SCI., 1930, 179, 477.
9. Hymen, H. T., and Kessel, L.: J. Am. Med. Assn., 1927, 88, 2032.
10. Means and Richardson: Oxford Monographs on Diagnosis and Treatment, 1929, 4, 131.
11. Eberts, E. M., Fitzgerald, R. R., and Silver, P. J.: Surgical Treatment of the Thyroid Gland, Lea & Febiger, Philadelphia, 1929, pp. 97 and 178.
12. Davis, C. H.: J. Am. Med. Assn., 1926, 87, 1004.
13. Phemister, D. B.: Personal communication.

LOW BASAL METABOLISM FOLLOWING LOBAR PNEUMONIA ASSOCIATED WITH MARKED UNDERNUTRITION.

BY A. H. GORDON,

ASSOCIATE PROFESSOR OF MEDICINE, MC GILL UNIVERSITY,

AND

I. M. RABINOWITCH,

ASSISTANT PROFESSOR OF MEDICINE, MC GILL UNIVERSITY, MONTREAL, CANADA.

(From the Medical Service of Dr. A. H. Gordon and the Department of Metabolism,
The Montreal General Hospital.)

It has been known for some time that undernutrition may result in lowering of the basal metabolic rate. The literature on this subject is large and there are a number of excellent reviews. For purposes of brevity, therefore, only relevant facts will be here referred to.

Experimentally, the metabolic rate of man or animal can readily be lowered simply by prolonged fasting. Clinically, as is well known, undernutrition may be caused by a variety of disorders, acute and chronic, such as fevers, malignancy, diabetes, peptic

ulcer, psychopathic states, etc. The exact mechanism by which the metabolic rate is lowered in such cases is imperfectly understood. Loss of body weight (decrease of protoplasmic mass) is not the only explanation, since the decrease of the basal metabolic rate may be much greater than the decrease of body weight. Whatever the cause of the low metabolism is, it appears, according to Lusk, to be a specific reaction and its purpose is protective, by lessening the demand for food. Though such reduction of metabolism is not often very great, ranging usually from 10 to 15 per cent, it sometimes may represent as much as one-third of the total metabolism. Thus in Benedict's fasting experiment, the decrease of metabolism was over 30 per cent on the twenty-first day of starvation, and Magnus-Levy's subject, who lived on a low diet for nine months, lowered his metabolic rate 33 per cent below the average. Very low metabolic rates have been found more often in chronic than in acute conditions. The case reported here is, therefore, of interest not only because the nutritional disorder was acute, but particularly because of the extremely low basal metabolic rate. The clinical data are, briefly, as follows:

Case Report.—A Norwegian male (Hosp. No. 617-30), thirty years of age, was admitted on January 31, 1930, with a history of pain in the chest of five days' duration, accompanied by cough and chills. The family and personal histories were irrelevant.

On admission the condition from which he was suffering was a left lobar pneumonia caused by *Pneumococcus* Type II. The findings were otherwise negative, with the exception of some thyroid enlargement, exophthalmos and a positive van Graefe (eye) sign.

On the day of admission, the temperature ranged between 104° and 105° F., the pulse rate between 102 and 124 and the respiration rate between 32 and 36 per minute. Besides the usual routine measures, he was given Felton's pneumococcus antibody solution, of which 70,000 units were administered during the first forty-eight hours. On the third day, the temperature was normal for a short time, but returned again for a day to a higher level, ranging between 100° and 101°. On February 7, the twelfth day of the disease and eight days after admission, the temperature, pulse and respirations were normal. The clinical course, thereafter, was uneventful. On February 14, he was allowed out of bed and was weighed the following day. He then weighed 138½ pounds and volunteered the statement that he had lost 20 pounds since commencement of his illness.

On February 22, as a matter of curiosity, because of the exophthalmos and thyroid enlargement, the basal metabolic rate was determined and was found to be -40. As the result was remarkable, a detailed investigation was made with regard to it. No errors were found, technical or otherwise; the test was performed with the Benedict-Roth apparatus, measuring the consumption of oxygen only, since no marked alterations of the respiratory quotient were expected. The test was done in triplicate with uniform results. The patient's attitude throughout the test was quiet and his co-operation was very good. A striking feature which corresponded with the result of the test was the slow pulse rate. In our routine, we determine the pulse rate immediately before records are taken, during the test and immediately after. These rates were 44, 46 and 44 beats per minute respectively. The temperature was 97.8°. On this day he weighed 141 pounds.

METABOLISM DATA.

Date (1930).	Calories per hour.	Body weight (kg.).	Body surface* (sq. M.).	Du Bois.		Harris-Benedict.		Boothby-Sandiford.		Average B. M. R. (per cent).	Pulse-rate (beats per minute).			Attitude of patient.	Coöper- ation.
				Standard calories per hour.	B. M. R. (per cent).	Standard calories per hour.	B. M. R. (per cent).	Standard calories per hour.	B. M. R. (per cent).		Before.	During.	After.		
Feb. 22 . .	42.0	64.1	1.84	72.6	-41	69.1	-39	71.8	-42	-40	46	44	44	Quiet	Good
Feb. 25 . .	44.6	65.4	1.85	73.0	-39	69.7	-36	72.1	-38	-38	50	50	50	"	"
Mar. 1 . .	51.0	65.8	1.86	73.5	-31	70.1	-28	72.5	-29	-29	54	52	58	"	"
Mar. 7 . .	76.0	66.8	1.87	73.8	+3	70.6	+7	73.0	+4	+5	62	62	62	"	"
Mar. 11 . .	75.0	67.3	1.87	73.8	+1	70.8	+6	73.0	+3	+3	58	64	64	"	"

* Height = 183 cm.

Because of the extremely low basal metabolic figure found, the test was repeated three days later. The result was -38 . The patient again co-operated very well and was quiet through the test. The pulse rates were again remarkably constant and low, namely, 50, 50 and 50 respectively and the temperature was 97° . The weight now was 144 pounds.

In view of the exophthalmos and large thyroid, a possible explanation of the low metabolic rate was that this patient had hyperthyroidism sometime previously and that he is now suffering from myxedema. There was, however, no history to suggest a previously existant hyperthyroidism and there are now no clinical signs nor symptoms to indicate myxedema. It was, therefore, suggested that the cause of the low basal metabolism was the undernutrition which resulted from his present illness; as he had lost about 20 pounds very rapidly. If the latter was the correct explanation, the basal metabolic rate should recover with the recovery of the general nutrition. He was, therefore, kept in the hospital for further study and the accompanying table shows the combined results.

All basal metabolic rate determinations were carried out exactly under the same conditions. At each test, the coöperation was very good and the attitude was quiet. In order to avoid vagaries due to standards, three different types were used, namely, Du Bois, Harris-Benedict and Boothby-Sandiford and the average of all three was taken.

The special features to be noted are: (a) The pulse rate corresponding to the basal metabolic rate; (b) the relatively rapid recovery of body weight; (c) the recovery of the basal metabolism to the normal level at a rate greater than recovery of body weight, and (d) the tendency toward low temperature.

While all these changes were taking place in the basal metabolism the only noticeable clinical reaction was the general improvement in health. A rather interesting feature is the remarkably rapid recovery of the basal rate to the normal level between March 1 and March 7. The explanation of this phenomenon which we suggest is that we are dealing with a disease characterized by marked and rapid fluctuations of metabolism. For example, probably no other disease manifests such marked changes as may be found in an individual with pneumonia between twelve hours before and twelve hours after the crisis.

Another factor which might be considered is the use of Felton's solution. As far as we have been able to ascertain, no observations have been made with regard to the effects of this form of therapy on the basal metabolism, which may be considerable. This, however, is only a suggestion for further study. It is our opinion that undernutrition was the dominant feature of the altered metabolism in this case.

Summary. This case of convalescent lobar pneumonia is of special interest because of the extremely low basal metabolic rate found, and the fact that the undernutrition was of an acute, rather than of a chronic, form.

NOTE.—Grateful acknowledgement is due Miss Phyllis Holroyde for the careful basal metabolic rate determinations.

METASTATIC ABSCESES OF THE BRAIN.

A CLINICAL STUDY.*

BY HARRY L. PARKER, B.A., M.B.,

ASSOCIATE IN SECTION ON NEUROLOGY, THE MAYO CLINIC; ASSISTANT PROFESSOR OF
NEUROLOGY, THE MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH,
GRADUATE SCHOOL, UNIVERSITY OF MINNESOTA, ROCHESTER, MINN.

THE unexpected, sudden appearance of symptoms in suppurative disease of the nervous system, the rapid unfolding of the clinical picture, the puzzling periods of fluctuating signs and, above all, the domination of the more obscure nervous manifestations by the general picture of sepsis, constitute factors that may be bewildering and confusing as well as obstructive to an intelligent comprehension of the problem at hand. In going over a series of cases of intracranial suppuration secondary to sepsis elsewhere in the body, attempts have been made to find, if possible, some common factors. Unfortunately, this is not easy, since each case is almost a law unto itself and markedly individual in its characteristics. There is so complex a panorama of events that infinite variation is possible. Even when traced back from the final stages of the disease, namely, death or cure by operation, the steps in the progress of the infection may be impossible to delineate. Notwithstanding these difficulties and largely because of them, a series of 20 cases was studied in which the suppuration in the brain came from a source elsewhere in the body. They were all proved cases. The diagnosis was proved by necropsy in 18 cases and in 2 by surgical exploration. Because of the marked differences in the cases and in order to get a better comprehension of the whole problem, the cases will be considered under three group headings. It would seem that since the suppurative process in the brain is secondary to a cause elsewhere in the body, emphasis must be laid on the original source of the infection and the cases grouped accordingly. From the pathologic, as well as the prognostic point of view, it has also seemed fitting to consider the cases in the order of the severity of the original infection at the time the patient was observed. In the 3 cases in Group 1, the cerebral abscess was only part of an overwhelming general septic process; in the 14 cases in Group 2, the abscess was secondary to pulmonary or pleural suppuration which may or may not have been in the process of healing, but in any event did not immediately menace life, and in the 3 cases in Group 3, perhaps the most significant clinically, the original infection had run its course, and the process had healed and would have been forgotten but for the signs of cerebral abscess that appeared later and constituted the most striking feature.

* Read before the Chicago Neurological Society, Chicago, Illinois, April 17, 1930.

Group 1. Metastatic Abscess of the Brain Secondary to General Sepsis With Endocarditis. In these cases there is either a rapid, virulent septicemic condition with organisms in the blood stream, endocarditis and multiple embolic abscesses and finally death in a short time from the general infection, or there is a slower process of septic destruction in which complication after complication arises and finally the patient dies from the cerebral abscess, a last and more lethal manifestation of a long-continued process. In either case the cerebral abscess is only one episode in a general septic process. Any one of the other complications would probably have been fatal eventually. These cases, therefore, are of relatively less clinical interest and more of pathologic interest. In cases of pyemia with multiple septic emboli, as a matter of fact, the brain is seldom affected. This will be commented on later in considering cerebral abscess secondary to suppuration of the lung. A case illustrative of those in Group 1 follows:

Case Abstract. CASE I (Table I).—A man, aged fifty years, was brought to The Mayo Clinic October 16, 1923, because of convulsions and mental confusion. Five months before, a wound in the right index finger had become infected. The infection spread to the palm and incision and drainage became necessary. Fever of 104° F. occurred, and fourteen days after the onset redness and swelling suddenly appeared in the right calf which did not go on to formation of abscess but subsided spontaneously after about five weeks. The patient was confined to bed because of continued fever and weakness. Frequency and pain on urination were next complained of, and loss of weight and strength continued for two and a half months. At the end of this time and two months before admission he had had a series of general convulsions. Four days later a large perinephric abscess was opened and drained. The temperature diminished and gradually became normal, but convulsions continued and four days before admission he became clouded mentally.

The patient appeared ill and emaciated and was in a state of semistupor. The urine contained pus and blood. There was a discharging sinus in the right flank. The blood count showed a moderate degree of anemia. Pulse, temperature, leukocytes and spinal fluid were nevertheless normal and there was no papilledema. Babinski's sign was positive on the left side. Following spinal puncture the patient improved, became rational and was able to sit up in bed. Another series of convulsions supervened, however, and left hemiplegia rapidly developed with return of the stupor which deepened progressively. In spite of a general enfeebled condition, as a last resort a trephine opening was made over the right frontotemporal area and about 45 cc. of thick, yellow pus was evacuated. The patient again improved for a while but signs of meningitis developed and he died eight days after the operation.

Necropsy showed a group of chronic encapsulated abscesses of the right frontal lobe of the brain with terminal rupture into the right lateral ventricle and suppurative meningitis. A healed area of aortic endocarditis, a healed infected wound of the right hand, and multiple abscesses of the kidneys, prostate gland and perinephric tissues were noted.

This case illustrates one end of the scale of chronicity. The abscesses were in a cluster and one had ruptured into the ventricle

causing the terminal picture. Nevertheless, the abscesses were fairly well encapsulated, apparently chronic, and corresponded to the rate of the progress of events. On the other hand, the course of the patient was steadily downhill, and he was emaciated and exhausted from sepsis when the abscess was operated on. Any other phase of the septic condition might have been fatal. Case III (Table I), it may be noted, was equally as hopeless from the beginning but ran a much more rapid and remorseless course to the end. The 3 cases in this group showed evidence of endocarditis with ample possibilities for widespread infection. In all 3 the abscesses were multiple; in Case I the abscesses were clustered in a group in the anterior end of the right frontal lobe and in Cases II and III they

TABLE I (GROUP 1).—METASTATIC ABSCESS OF THE BRAIN SECONDARY TO GENERAL SEPSIS WITH ENDOCARDITIS.

Case.	Association infections.	Duration of illness.	Clinical course of cerebral complications.	Duration before death.	Necropsy data.
1	Infected right index finger, lymphangitis, perinephric abscess	Five months	Convulsions, increasing in frequency, rapid left hemiplegia; trephined	Two months	Multiple right frontal abscesses, aortic endocarditis; abscesses of kidneys.
2	Diverticula of bladder, cystitis, pyelonephritis	Twelve months	Drowsiness, increasing stupor; death without localizing signs	Eight days	Multiple abscess of brain, mitral endocarditis with embolic abscesses.
3	Acute osteomyelitis, right tibia	Eleven days	High fever and marked toxemia covering all other signs; rigidity of neck toward end	Eleven days	Multiple small abscesses of kidneys and brain, early meningitis.

were small embolic abscesses strewn indiscriminately in both hemispheres and in the cerebellum. Localization was possible in only one of the 3 cases. In the other 2 cases, the patients were so profoundly ill that the cerebral symptoms were identical with those found in any acute toxic process and not necessarily characteristic of local suppuration of the brain. As causes of these pyemic abscesses, Oppenheim mentioned ulcerative endocarditis, phlegmonosis, suppuration of bones or joints, whitlow, carbuncle, septic endometritis, endamebic abscess of the liver and suppurating bronchial glands. Otitis media with or without mastoiditis and septic sinus thrombosis may do the same thing; hence abscess of the brain remote from the side of the affected ear. As is reasonable to assume, any septic process producing pyemia can be a source for multiple cerebral abscess.

As I have mentioned, it has been observed that the brain has a relatively higher resistance to infected emboli from sources other

than the lung. Actually such abscesses are uncommon. Sperling in 76 cases of emboli from the left side of the heart, found that metastatic abscess occurred in the kidneys in 57, in the spleen in 39 and in the brain in 15 only. On the other hand, suppuration of the lung is more often the cause of metastatic abscess of the brain than of abscesses elsewhere. In this series of 20 cases 14 (Group 2), were secondary to pulmonary suppuration.

Group 2. Metastatic Abscess of the Brain Secondary to Pulmonary and Pleural Suppuration. In this group the original infective process is serious but not so deadly, and not infrequently it happens that the cerebral abscess constitutes a lethal complication causing death of a patient who might have otherwise recovered. Cases have been reported by Roulland, Seymour, Barling and Hurst and Gardner in which surgical drainage of both brain and lung saved the patient. Too often, however, the patient has had a long siege of disease, is markedly exhausted and his vitality is at a low ebb. An abscess developing in such a case meets little resistance and responds only slightly to surgical drainage. The following case is a good example of this group.



FIG. 1 (Case VIII).—Metastatic abscess of the left parietal lobe of the brain secondary to pleural empyema. The abscess is fairly well encapsulated but is surrounded by a wide zone of softening. Rupture into the left lateral ventricle.

CASE XIV (Table II).—A boy, aged eighteen years, came to The Mayo Clinic September 17, 1923, because of cough, weakness and a draining sinus of the left wall of the thorax. Seven years before admission he had accidentally inhaled a brass carpet tack. A sense of strangulation immediately was felt with paroxysmal coughing. The cough continued and the patient lost weight and strength, bringing up foul sputum in increasing

amounts. One year previously the left lung had been explored in a two-stage operation, but the tack was not recovered and the draining sinus persisted.

The patient appeared thin, weak and pale; the odor of his breath was foul. His fingers were clubbed. He had a fever of 101° F. A sinus was draining in the left posterior wall of the thorax. Roentgenograms showed bronchiectasis of the left lower lobe and a tack in the left lower part of the bronchus. Bronchoscopy was done and an attempt was made to remove the tack through a bronchoscope but it failed. The lung was explored September 25, 1923, and through a cautery incision the tack was removed. The patient recovered from the immediate effects of the operation but a bronchial fistula persisted with a sinus in the wall of the thorax still draining. He continued to cough up large quantities of sputum. He did not gain strength, and during the following year two other exploratory operations were performed on the thorax and lung in the hope of leading to the closure of the bronchial fistula and sinus. Six days after the second operation, he suddenly felt that his right leg was powerless and then there was a jerking feeling in the right lower wall of the thorax with immediate loss of consciousness and general convulsions. Other attacks followed and he was readmitted to hospital. In a few days weakness of the right arm and leg appeared and he became stuporous and aphasic. His eye grounds were normal. Leukocytosis was present; he ran an intermittent fever, became more stuporous, comatose and died ten days after the first onset of cerebral symptoms.

Necropsy showed a solitary abscess 5 by 5 cm. in the left parietal lobe which had ruptured into the left lateral ventricle. The brain was markedly softened around it. Fig. 1 is illustrative of a similar case.

The relative frequency of metastatic cerebral abscess secondary to suppurative pulmonary or pleural disease has been commented on by all the writers on the subject as well as has the curious predilection of the brain for these abscesses in advance of any other organ in the course of pulmonary disease. Why the brain should be more frequently affected than other organs has been always a puzzling question. The relative infrequency of the formation of abscess in diffuse septic conditions with endocarditis, as mentioned, makes the problem harder to solve. Shorstein suggested that in acute infective diseases the brain has a relatively greater resistance to infective emboli. In chronic suppurative pulmonary disease, on the other hand, the chronicity of the process has allowed the remainder of the body to develop antibodies which the brain fails to do for some unknown reason. Eagleton tried to explain the phenomenon by asserting that the metastatic cerebral abscess from disease of the lungs is primarily of venous and thrombotic origin, as contrasted with abscesses of arterial or embolic origin from endocarditis. Disease of the lungs, he believes, would favor this thrombotic process in the cerebral veins. Gardner suggested that long-continued coughing has an influence. Such straining produces positive intrathoracic pressure, a damming back of venous blood, less filling of auricles, poor cardiac output and transient ischemia of areas in the brain. This tends to lower cerebral resistance to infection. Groth also invoked some mechanical factor in the cir-

culuation induced by disease of the lungs and continued coughing. It may be remembered that a similar phenomenon is seen in carcinomatous metastasis. Carcinoma of the lung frequently metastasizes to the brain and yet the brain is specially resistant to metastasis in general carcinomatosis from other organs. It is manifestly possible that the tissue of the lungs and brain have something in common whereby the brain tissue acts as highly favorable soil for metastasis thrown off from suppurative or carcinomatous processes occurring in the lungs. The problem must be considered as unsolved until more work has been done on the subject.

The cases of cerebral abscess secondary to disease of the lungs and pleura have been arbitrarily divided into various types, those secondary to empyema and those secondary to bronchiectasis and abscess of the lungs. This division is actually rather artificial. The pathologic boundaries of abscess of the lungs, bronchiectasis and empyema are not always definite. In a given case an abscess of the lung may lead to bronchiectatic enlargement of adjacent bronchi; it may rupture into the pleural cavity and form empyema. This may be drained and a combination of abscess of the lungs, bronchiectasis, bronchial fistula, empyema and sinus in the wall of the thorax may be the final clinical picture. Again an empyemic abscess may rupture into a bronchus, and bronchiectasis may form with bronchial fistula. Seldom, if ever, is the lung normal under a chronic empyema cavity, and actually these combinations occurred in many of the cases which form the basis of this report. Accordingly, no attempt has been made to separate the cases due to empyema from those due to bronchiectasis or abscess. Figures, therefore, regarding the frequency of association between the various diseases of the lung and cerebral abscess are subject to criticism. Those of Schorstein are drawn from a relatively large group of 69 cases (19 of his own) of metastatic cerebral abscess associated with suppurative disease of the pleura and lung. In these, bronchiectasis occurred in 38 (55 per cent), empyema in 15 (23 per cent), gangrene of the lung in 6 (9 per cent), and the remaining 10 were evenly divided: tuberculosis, 3; acute pneumonia, 3; abscess of the lung, 2; fetid bronchitis, 1, and emphysema and bronchitis, 1. Schorstein stated that bronchiectasis is the most common pulmonary antecedent of cerebral abscess, and cerebral abscess is the second most common cause of death in bronchiectasis. Cerebral abscess secondary to ulcerative pulmonary tuberculosis is not common; I have, however, seen one case. Another disease of the lungs as a possible cause of cerebral abscess is actinomycosis. There is one of these in the records of The Mayo Clinic. However, it has not seemed advisable to include such granulomatous and mycotic diseases in the present study.

Because of the complexity of the problem, it has been hard to illustrate the common features of the 14 cases of abscess of the

brain secondary to suppuration of the lungs. Signs prominent in one case may be absent in others, and it is difficult to determine which sign is the most significant. Again, infection is a moving process; conditions resembling one another one day may present totally different appearances the next. However, it has been thought best to chart a general panoramic version of each case with the time relations (Table II). Symptoms are mentioned in order of occurrence and a glance may show the general trend of events. The history of many of the cases indicated extreme chronicity of pulmonary symptoms. In the foregoing case (Case XIV) the patient had been

TABLE II (GROUP 2).—METASTATIC ABSCESS OF THE BRAIN SECONDARY TO PULMONARY AND PLEURAL SUPPURATION.

Case.	Clinical course of cerebral complications.	Duration before death.	Necropsy data.
4	Gradual right hemiparesis, stupor, fever, rigidity of neck, purulent spinal fluid	Eight days	Solitary abscess, left frontal lobe, ruptured.
5	Headaches, vomiting, mental confusion, stupor, rigidity of neck, purulent spinal fluid	Three weeks	Solitary abscess, right frontal lobe.
6	Stupor, rigidity of neck	Four days	Solitary abscess, right thalamus.
7	Headache, right temporal region, vomiting, stupor, rigidity of neck, purulent spinal fluid	Eight days	Solitary abscess, right temporal lobe, ruptured.
8	Headaches, weakness right arm, aphasia, fluctuating course, stupor, craniotomy	Nine days	Solitary abscess, left frontoparietal region.
9	Headaches, Jacksonian convulsions, right hand and arm, increasing right hemiplegia and aphasia, craniotomy, stupor	Three weeks	Multiple abscesses of the brain.
10	Headaches, increasing stupor	Six days	Multiple abscesses of brain, ruptured.
11	Delirium, stupor, rigidity of neck, purulent spinal fluid	Few hours	Multiple abscesses, ruptured.
12	Headaches and fever for three days, patient found dead in bed	Three days	Solitary abscess, right parieto-occipital lobe, ruptured.
13	Jacksonian convulsions and gradual right hemiparesis, improvement for few weeks, then suddenly worse	Three months	Solitary abscess, left parietal lobe.
14	Convulsions with right motor aura, rapid development of right hemiplegia with aphasia	Ten days	Solitary abscess, left parietal lobe.
15	Sudden general convulsion, recurred at frequent intervals, gradual left hemiplegia	Two months	Multiple abscesses of brain.
16	Increasing headaches, drowsiness and stupor	Three days	Multiple (more than 50) abscesses of brain.
17	Operation for left mastoiditis, lighting up of old lung infection, sudden stupor with right hemiplegia	Fifteen days	Multiple abscesses of brain.

sick at least seven years. The average total duration of illness in the 14 cases was thirty months. In 12 of the cases one or more operations had been done on the pleura and lung, and in 10 abscess of the brain had developed during convalescence from the last operation. The occurrence of cerebral abscess has been attributed to operative procedures on lungs and ribs, but experience has shown this to be wrong. Schorstein denied any such relationship. He pointed out that in many instances cerebral abscess develops long after, sometimes many months after, the surgical procedures, such as resection of ribs. The abscess frequently occurs in cases in which the opening in the wall of the thorax has never properly closed and a more or less continuous purulent discharge has been kept up. This occurred in 9 of the series of 14 cases. Cerebral abscess may also occur in cases in which no operation has been performed, or in which simple aspiration of an empyemic abscess has been done. Bronchiectasis, whether or not operation is performed, constitutes a continuous menace from the standpoint of this complication.

There was a preponderance of the male sex, in the 14 cases of the series, 13 to 1. Age made little difference; the patients varied from the first to the seventh decade. Eleven patients were in the third to the sixth decade. From the symptomatic standpoint there is little difference between metastatic abscess of the brain and abscess due to other causes. As Schorstein noted, nothing materially new can be drawn from an analysis of symptoms. These abscesses of the brain developed in cases in which the patients were exhausted by long illness, and the abscess, once started, seemed to run a rather acute course. In his 19 cases the average duration of illness from the initial sign of cerebral disease to death was ten days; the illness varied between three and twenty-eight days. In these 14 cases nineteen days was the average; the illness varied from three months to a few hours. Most of the patients lived only a few days after evidence of cerebral involvement appeared. In one case only (Case XIII) was there evidence clinically of a latent period. Table II shows the order of development of symptoms. In 7 of the 14 cases the onset was gradual and the symptoms were of the usual type in cases of abscess of the brain, namely headache, vomiting, local or general convulsions, drowsiness, paralysis and coma. The particular feature of these metastatic abscesses was the rapidity of the course. One patient died a few hours from the onset of symptoms; the abscess had ruptured. One patient was found dead in bed after three days of headache and fever. Three patients had an abrupt and sudden onset with general or Jacksonian convulsions, and one patient had sudden hemiplegia and stupor. One patient suddenly became stuporous; the clinical picture of meningitis appeared, the abscess ruptured and death occurred four days after the onset.

Eight of the patients when first examined had fever and rapid

pulse rate: 3 ran a subnormal temperature and slow pulse and 3 had normal pulse and temperature at the beginning. In 10 of the 13 cases in which a blood count was made, there was leukocytosis. Most of the patients were septic in appearance and suggested some type of spreading infection. It is significant that papilledema was not present in 10 cases in which an ophthalmologic examination had been made. This may suggest that the abscess in each case destroyed tissue as it spread; in many cases wide zones of softening surrounded the abscess. Symptoms were therefore less due to pressure than to a wide encephalitic and disintegrating process. Clinical localization was only possible in 8 cases, but in 4 of these there were multiple abscesses. In 2 cases the abscesses were in the parietal lobe and gave signs suggesting their presence in the frontal lobe. In explanation it was found at necropsy that massive infarcted areas had spread well into the frontal lobe. Spinal puncture was done in 6 cases and purulent fluid was found in five. In all of these cases the abscess had ruptured. A correct diagnosis of abscess of the brain was made in 11 cases; in one case none was recorded and in one case embolic encephalomalacia was given as the cause of death.

In 7 of the cases with cerebral abscess secondary to suppuration of the lungs, the abscess was solitary and in the other 7 more than one abscess was found at necropsy. This agrees with the figures of Gowers, that 46 per cent are solitary, and with those of Eagleton, who, after reviewing the literature of the preceding twenty-five years, thought that 45 per cent of all metastatic abscesses are solitary. Schorstein, however, estimated that in the 51 cases which he reviewed, 32 (62 per cent) of the abscesses were multiple and 19 were single. In my series neither side nor any one lobe of the cerebral hemispheres seemed predominantly implicated. It has been assumed that the left side is the most frequently involved, but any part of the hemispheres may be attacked. The cerebellum was not affected in any of the cases of these abscesses secondary to pulmonary suppuration.

From the standpoint of prognosis and more especially from the possibility that these abscesses may be treated successfully by operative procedures, several factors must be taken into consideration, and first and foremost of these is the physical condition of the patient. Most of these 14 patients were considerably debilitated from long-continued pulmonary or pleural suppuration and multiple operations for relief. These factors elevate the risk of mortality but are not necessarily insuperable obstacles to successful surgical treatment. Enough patients who have been operated on have recovered in spite of the heavy hazard to make an attempt to drain the abscess well justified, provided other factors permit. These are represented in the frequent lack of information leading to accurate clinical localization as well as the possibility of multiple abscesses, of which there is always a 50 per cent chance. Only 7 of the patients in this

group had a single abscess, thereby ruling out the other 7 from all chance of surgical relief. Five of the 7 patients with solitary abscess had grossly and microscopically a fairly well defined capsular wall. With this, one might prognosticate a fair chance for successful drainage. However, only 4 patients of those with solitary abscess manifested signs to indicate where intracranial exploration might be attempted. The other 3 had nothing to indicate which side or lobe of the brain should be explored. Two of the patients manifested clinical signs suggesting the site in the frontal lobe; necropsy revealed an abscess considerably more posterior in the parietal lobe and had exploration been attempted the abscess might have been missed. Again the stage of development of the abscess is important. A few patients were first seen when it was obviously too late to institute treatment. High fever, rapid pulse, leukocytosis, rigidity of the neck and purulent spinal fluid are signs of evil portent, for they indicate rupture of the abscess into the ventricle and an end to all hope of saving the patient. In 4 cases there was good clinical evidence of the site of the abscess, but in 1 case (Case VII) rupture had evidently occurred before the patient was first seen. Three cases, therefore, remain out of the series of 14 of metastatic abscesses secondary to pulmonary disease that were in any way favorable for operation. In one of these (Case VIII) operation was performed and the abscess was drained successfully, but death occurred and necropsy showed a large area of infarction around the abscess. One of the other 2 patients (Case XIII) could possibly have been saved but for the mistaken diagnosis of embolic infarction with encéphalomalacia. In the other case (Case XIV) a solitary abscess was fairly well localized but operation was not performed because of the patient's poor general condition. Rupture of the abscess occurred a few days before death and while the patient was under observation. The whole course of cerebral symptoms in this case only lasted ten days. At necropsy little, if any, encapsulation was evident and the abscess was surrounded by a large area of softening. Altogether these cases do not carry a happy prognosis, but it is possible in a suitable case to save the patient. Favorable signs would be a history of relatively long-standing cerebral trouble, good physical condition and sufficient evidence for clinical localization. Contraindications to operation would be evidence of multiplicity of abscesses or signs of rupture into the ventricles.

Group 3. Metastatic Abscess of the Brain Secondary to Infection That Had Subsided. This group differs from Groups 1 and 2 from the standpoint of prognosis and features in the histories. An illustrative case follows:

CASE XIX (Table III).—A man, aged forty-two years, first came to The Mayo Clinic July 20, 1924, because of convulsive seizures. March 3, while lifting a heavy object, he had felt pain in the left lumbar region. This persisted and three weeks later frequency and difficulty in urination

appeared. This increased and examination of the urine, May 13, disclosed a large amount of pus. He had had chills, fever and leukocytosis, and a diagnosis of cystitis and pyelitis was made. Treatment was instituted and the trouble subsided. While convalescing from this about a month before admission, and after the acute phase of the urinary infection, a convulsive attack had come on without warning and while he was sitting quietly reading. Another similar convulsion appeared a week later; this led to his coming to the clinic.

The results of examination of the urine, the eye grounds and spinal fluid, and the leukocyte count were negative. A diagnosis could not be made and the patient was sent home for further observation. He returned August 30, and complained that soon after leaving the clinic severe occipitotemporal headache had appeared and during its maximal severity the pulse was slow.

Examination at this time disclosed slight papilledema of the optic disks, horizontal nystagmus and left homonymous quadrant defect for colors in the visual fields. A diagnosis was made of tumor of the right temporal lobe of the brain and craniotomy was advised.

September 5, a heart-shaped tumor, 5 by 3 cm. was removed. It was attached to the dura and situated in the posterior temporal area of the brain on the right side. There was some brain tissue over the surface of the tumor but no great difficulty was encountered in removing it. Section and microscopic examination showed the tumor to be an abscess with dense thickened walls. The patient recovered from the operation, and is living and performing his usual work six years after operation. The only trouble he has is an occasional convulsive attack about twice a year.

TABLE III (GROUP 3).—METASTATIC ABSCESS OF THE BRAIN: ORIGINAL INFECTION APPARENTLY HEALED; LONG LATENT PERIOD.

Case.	Original infection.	Duration of illness.	Clinical course of cerebral complications.	Duration before death.	Necropsy or operation
18	Osteomyelitis, left elbow, shoulder, right scapula	Four years	Headaches four months, vomiting, prostration, stupor last six days, terminal hemiplegia and coma	Four months	Head only, solitary abscess, right parieto-occipital lobe, ruptured.
19	Cystitis and pyelitis	Six months	Convulsions, headaches, choked disks, field changes		Craniotomy, removal encapsulated abscess <i>in toto</i> , right temporal lobe.
20	Infected teeth (extraction)	Five months	Convulsions, headaches, vomiting, stupor, weakness left side, choked disk		Craniotomy, drainage abscess right frontal lobe.

This case is fairly characteristic of the group and demonstrates the manner in which the cerebral symptoms develop. The symptoms occurred sufficiently long after the disappearance of the original infection to cause doubt as to whether they were associated with the later developments. The course of symptoms was, moreover, slow; in the 3 cases there was an average course of three and a half

months (Table III), a much longer period than in Group 2, in which the average course was nineteen days. Correspondingly at least 2 of the patients in Group 3 presented a picture completely different from those in Groups 1 and 2. After they recovered from the original infection they showed no signs of sepsis. Their color was normal, fever and leukocytosis were absent, and the cells in the spinal fluid did not increase. Moreover, papilledema was present and the general clinical picture led to a mistaken diagnosis of cerebral tumor rather than abscess. The first case in the group (Case XVIII) probably had presented such a picture earlier. Unfortunately, the abscess had ruptured into the ventricle shortly before the patient's admission to the clinic and he died seventeen hours after admission. It is possible that if the patient had been seen earlier a similar mistaken diagnosis might have been suggested, for the lesion from the original infection (osteomyelitis) had been apparently healed for four years, and the patient had been well and working during the interim. It would have required considerable imagination to connect this remote illness with the more recent trouble.

In Case XX simple uncomplicated dental extraction was associated with the serious condition of cerebral abscess. The patient had, however, a congenital lesion of the heart consisting of a patent interventricular septum and this in all probability supplied the missing link between cause and effect. Both Gowers and Schorstein have commented on this association. The former had no hypothesis to offer, the latter, after noting the frequency of this curious association between congenital heart disease and abscess of the brain, believes it may possibly be due to secondary change induced in the lungs by that condition. It is possible also that with a patent interventricular septum the lungs may be relatively short-circuited and a septic embolus may readily pass from the venous circulation to the arterial circulation and thence to the brain. Under normal conditions a septic infarct of the lung would be produced. In all 3 cases there is the mystery of a wandering embolus which reaches the brain and nowhere else, giving signs of mischief long after its source has been healed. A definite latent period was present in Cases XIX and XX and from the first convulsion, occurring as it did while the original infection was disappearing, to the definite progress of cerebral symptoms, there was an appreciable interval. In all 3 cases there was definite encapsulation. The capsule of the abscess in Case XIX was so thick and dense that even at operation it was mistaken for a tumor. Ballance mentioned a case of abscess similarly removed which was as round and hard as a billiard ball. From every standpoint these cases represented a better prognosis and actually the more the condition resembles that of cerebral tumor and the less there is which is suggestive of the formation of abscess the more hope is there for the patient. Generally speaking, the clinical syndrome of the cases in Group 3 suggests a diagnosis of

cerebral tumor since the original infection is much in the background, almost forgotten, and indicates little in the way of etiology until observations at operation or necropsy lead to a review in retrospect of the whole case.

Summary and Conclusions. Twenty cases of metastatic abscess of the brain were studied clinically. The diagnosis had been established either by necropsy or surgical exploration.

For convenience the cases were classified in three groups. In Group 1 were 3 cases in which the abscesses were secondary to an overwhelming or progressive general septic process; in Group 2 were 14 cases secondary to pulmonary or pleural suppuration, and in Group 3 were 3 cases secondary to an original septic process that had apparently healed but the signs of cerebral suppuration had appeared later and progressed to menace the life of the patient.

The prognosis depends entirely on the severity and progress of the original infection. In Group 1 the condition was hopeless. In Group 2 it was grave, but in some of the cases might have been modified by operation. In Group 3 surgical treatment at a favorable time was possible and the outcome favorable.

The course of metastatic abscesses of pleural or pulmonary origin was much shorter than that of abscesses due to other causes. This no doubt depended largely on the debility of the patient. The clinical signs and symptoms, however, differed little. The severity of the original infection added a complicating feature, often making the diagnosis extremely difficult.

In 10 of the 20 cases a single abscess was situated in one or the other lobe of the cerebrum. In many of these a certain degree of encapsulation was present but rupture into the ventricle nevertheless occurred readily. In the other 10 cases the brain was the seat of multiple foci of suppuration.

BIBLIOGRAPHY.

1. Ballance, C.: Quoted by Oppenheim.
2. Barling, S.: A Case of Cerebral Abscess Complicating Abscess of Lung; Operation and Recovery, *Lancet*, 1917, i, 121.
3. Eagleton, W. P.: *Brain Abscess*, New York, Macmillan Company, 1922, p. 68.
4. Gardner, W. J.: Metastatic Abscesses of the Brain of Pulmonary Origin: a Report of 2 Cases, *Arch. Neurol. and Psychiat.*, 1928, 19, 904.
5. Gowers, W. R.: *Diseases of the Nervous System*, Philadelphia, P. Blakiston's Son & Co., 1888, pp. 851.
6. Groth, W.: Quoted by Eagleton.
7. Hurst, A. F.: A Case of Cerebral Abscess Complicating Empyema; Operation and Recovery, *Lancet*, 1925, i, 605.
8. Oppenheim, H.: *Textbook of Nervous Diseases*, Edinburgh, T. N. Foulis, 1911, 2, 856.
9. Roulland, H.: Abscès métastatique du cerveau au cours d'une suppuration pleurale; trépanation, drainage de l'abcès, guérison, *Paris chir.*, 1917, 9, 613.
10. Schorstein, G. I.: Abscess of the Brain in Association with Pulmonary Disease, *Lancet*, 1909, 18, 843.
11. Sperling: Quoted by Eagleton.

REVIEWS.

ANATOMY OF THE HUMAN BODY. By HENRY GRAY, F.R.S. Revised and re-edited by WARREN H. LEWIS, B.S., M.D. Pp. 1391; 1232 illustrations. Twenty-second edition. Philadelphia: Lea & Febiger, 1930. Price, \$10.00.

"SEVENTY-TWO years ago Henry Gray published the first edition of his *Anatomy*, the best known work in all English medical literature and by far its greatest textbook. Since then more doctors have learned their anatomy from Gray than from all other anatomical texts combined. The student does not discard his Gray. He takes it over into active practice as the cornerstone of his library and a constant source of reference, whether he be a surgeon or a medical practitioner. The use of the B. N. A. nomenclature in English has been retained practically unchanged in this edition and important references to the literature have been added at the end of each section. As a practical work on the subject for the student, Gray's *Anatomy* has always been recognized and appreciated. The plan originally formulated, which has proved so successful, has been adhered to as much as possible. It is interesting to note that although Henry Gray saw only the first edition, much of the original text persists and many of his illustrations are still in use. Bearing this in mind it has been the endeavor of the Editor to supply only such changes as advances in the science made necessary in order that this work may reflect the latest accessions of anatomical knowledge."

FEEDING IN INFANCY AND CHILDHOOD. By I. NEWTON KUGELMASS, M.D., PH.D., Sc.D. Pp. 345; 37 illustrations. Philadelphia: J. B. Lippincott Company, 1930. Price, \$6.00.

WRITTEN expressly for the general practitioner, this book has successfully attempted to explain the principles of infant nutrition in a practical and definite manner. The food requirements of infants are treated in respect to energy requirements, protein, carbohydrate, lipin, minerals, water and vitamin. Each of these needs is briefly discussed and explained where possible by tables or

schemata. The requirements of the infant as to the digestibility of its food are specially considered. The nutritive properties of various classes of dietary articles are commented upon separately.

The subjects of prenatal diet, prematurity, breast feeding and normal artificial feeding are clearly but very briefly discussed; the last named is reduced to a simple mathematical procedure, which is indeed proper for the practitioner. Separate sections are devoted to alimentary, deficiency, metabolic and so-called convulsive diseases, brevity, clarity and the free use of tables keeping the reader to the practical and concrete. Dietary management is outlined for infectious diseases, for heart diseases, pneumonia, tuberculosis, pertussis and other common conditions.

I know of no other work in which the author's knowledge has been so well reduced to the form of outlines and tables. His generous use of sample diets, of tables indicating caloric values, make it unnecessary to leave this book for such information. The Reviewer is pleased to compliment the publisher upon the appeal which this book makes to the eye, and to commend it most strongly to the general practitioner.

J. S.

TROPICAL MEDICINE IN THE UNITED STATES. By ALFRED C. REED, M.D. Pp. 410; 60 illustrations. Philadelphia: J. B. Lippincott Company, 1930. Price, \$6.00.

A KNOWLEDGE of the so-called tropical diseases, formerly little considered by the medical practitioner of temperate latitude, is becoming a more and more necessary part of his scientific armamentarium. Greater ease of travel has brought cases of exotic disease into all parts of the world. Moreover, a considerable part of the United States is practically subtropical and, therefore, suitable ground for spread of disease that may elude quarantine at seaports. Yellow fever in 1793 decimated the population of Philadelphia: *Aedes argutus* is still present in that region and could again take on its sinister rôle, should some national catastrophe break down quarantine barriers. What is more important, many tropical diseases are endemic in this country: for example, málaria, uncinariasis, amœbiasis, bacillary dysentery, pellagra, sprue and undulant fever.

Most works on tropical medicine are complete detailed treatises, planned to fulfill all the needs of those who practice medicine in the tropics. Yet their very completeness makes them rather unsatisfactory for physicians in higher latitudes, who consult such works only sporadically, and consequently fail at times to find the woods for trees. The author's book, on the contrary, is written expressly for physicians in the United States, avoiding unnecessary

detail as well as discussion of conditions never seen in this country (for example, African trypanosomiasis), yet presenting adequately all the necessary information on, and methods of, tropical medicine. The last chapter includes material on climatic conditions and personal hygiene in the tropics, useful for advising those who plan to go to those regions. The book is well written, well illustrated and has a convenient form and a pleasing makeup. R. K.

PERSONAL AND COMMUNITY HEALTH. By CLAIR ELSMERE TURNER, M.A., DR.P.H. Third edition. 443 pages; 62 illustrations. St. Louis. The C. V. Mosby Company, 1930.

THE book has been thoroughly revised. Much of the material of the former editions has been omitted and several new sections, including a chapter on Health Maintenance, have been added. Several new illustrations have been introduced.

The book has been prepared for the use of students of college grade and affords a good introduction to the fundamental principles of personal and community health.

The type, binding and illustrations are excellent.

D. B.

SURGICAL DIAGNOSIS, VOL. I. By 42 American Authors. Edited by EVARTS AMBROSE GRAHAM, A.B., M.D. Pp. 919; 508 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$35.00, set of 3 volumes.

THE first chapter on Wounds by Neuhof discusses wound repair and healing, and then takes up the diagnosis of various types of wounds, of bursæ, joints, nerves and bloodvessels.

Harvey's chapter on Infection is a veritable clinical bacteriology. He describes in a few words the laboratory characteristics of each organism and then more fully the pathogenesis and diagnosis of the diseases they cause. Included in this chapter are discussions of many of the common and even of the rarer parasites which occasionally produce surgical diseases.

The chapter on Postoperative Complications as written by Cutler and Scott is probably one of the most useful in the whole volume. It is presented in excellent form and is the more valuable because the authors suggest prophylactic and therapeutic measures for the complications they describe. At the end of each section is given a bibliography.

Diseases of Bloodvessels by Brooks is a chapter giving the general methods of use in diagnosis of blood vascular diseases and a discussion of the individual diseases. The writer draws largely from his

own clinical and experimental work, including also much from the works of Buerger, Matas and others.

Abbott gives full sections on Diseases of the Extremities, Bones, Cartilage, Tendons, Muscles, and so forth, and Koch and Kanavel present an excellent condensation of their well-known writings on Infections of the Hand. Hibbs writes on the diagnosis of the various lesions of the Spine, and the last portion of the volume is given over to a diagnosis of Fractures and Dislocations by Key. L. F.

AN INTRODUCTION TO VERTEBRATE EMBRYOLOGY. By H. L. WIEMAN. Pp. 411; 201 illustrations. New York: McGraw-Hill Book Company, 1930. Price, \$4.00.

THIS is a descriptive text intended primarily for premedical students. There are no laboratory directions as a separate laboratory guide has been published. After a short preliminary chapter there is an excellent discussion of the cytology of the somatic and sex cells, fertilization and cleavage. The results of modern lines of research, such as tissue culture, microdissection and chromosome study are all utilized. The early development of the organism is first described in *Amphioxus* and the frog. Then the embryology of the chick is followed out in considerable detail in 158 pages. To the Mammalian fetal membranes and the ontogeny of the pig and man are devoted 137 pages. The latter part necessarily becomes more sketchy. The author has wisely omitted following out the nervous system in the mammalian forms. It is described up to the three-day stage in the chick and that is sufficient to give a good idea of its early morphogenesis. Many of the illustrations are taken from recent studies and a six-page bibliography is appended.

W. A.

MEDICINE IN VIRGINIA IN THE SEVENTEENTH CENTURY. By WYNDHAM B. BLANTON, M.D. Pp. 337; illustrated. Richmond: The William Byrd Press, Inc., 1930. Price, \$6.00.

OF the various regional medical histories that have recently been appearing, none is worthier or more appropriate than the present volume under review. And in how many states would it be desirable or even possible to devote a large volume, as this one is, to the seventeenth century! The Medical Society of Virginia and its Historical Committee, under whose auspices the work was produced, may well be congratulated on the important contribution that has been made to American medical history. May the other two volumes that are contemplated maintain the excellence of subject matter and format and may they soon be forthcoming!

E. K.

BURNS: TYPES, PATHOLOGY AND MANAGEMENT. By GEORGE T. PACK, B.S., M.D., and A. HOBSON DAVIS, B.S., M.D. Pp. 364; 60 illustrations. Philadelphia: J. B. Lippincott Company, 1930. Price, \$6.00.

THIS book discusses a very important surgical subject which has not received the attention it so justly deserves. There are thirty-two chapters which are grouped into three parts: Part I: "Fundamental facts concerning Burns and Scalds," Part II. "The Management of Burns;" Part III. "Regional Burns—Burns by Specific Agents."

The entire book is a compilation of work already published in current literature. If a history of the subject is necessary it might have been made much more interesting. The statistical data are very interesting. The pathological and biochemical aspects are well handled. The chapters on treatment are disappointing. Surgeons now agree that the tannic acid method is the method of choice in treatment, and only four pages are given to it, while double that amount of space is given to the paraffin method, which is now rarely used. The book should prove useful as a reference text.

I. R.

CLIO MEDICA. VOL. II. MEDICINE IN THE BRITISH ISLES. By SIR D'ARCY POWER, K.B.E., F.R.C.S. (ENG.). Pp. 84; 1 illustration. New York: Paul B. Hoeber, Inc., 1930. Price, \$1.50.

THIS little book is an interesting addition to the "Clio-Medica" series on the history of medicine. The author reviews the history of medical and surgical practice as in the British Isles from medieval times to the present day. The origin of the early hospitals, St. Bartholomew's and St. Thomas' is interestingly described. The development of medical education from an apprentice system to that at present in use is outlined, and the reader will find an explanation for many anomalies of British medical organization. In addition brief accounts are given of some outstanding physicians of history from John Arderne (fourteenth century) to Lister.

H. B.

CHEMICAL METHODS IN CLINICAL MEDICINE. By G. A. HARRISON, B.A., M.D., B.Ch. (CANTAB.), M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 534; 65 illustrations. New York: The Macmillan Company, 1930. Price, \$5.25.

THE author discusses all the clinical chemical methods commonly used in the study of body fluids. Both quantitative and qualitative methods are given, together with their interpretation and application. There are twenty-six chapters, each dealing with another phase of the subject, a few of which might be mentioned: Reduc-

ing substances in the urine; interpretation of blood-sugar curves; ketosis, acidosis and alkalosis; blood and its derivatives in the urine; urines, abnormal in color; basal metabolism and metabolism experiments. The subject matter is presented briefly and to the point. At the beginning of each chapter there are given the references employed. At the end of the book there is a full index. The book contains much useful knowledge for the clinician and laboratory worker and is recommended to both. L. J.

KRANKHEITEN UND HYGIENE DER WARMEN LÄNDER. By PROF. DR. REINHOLD RUGE, PROF. DR. PETER MÜHLENS and PROF. DR. MAX ZUR VERTH. Pp. 494; 496 illustrations. Third edition. Verlag, Leipzig: Georg Thieme, 1930. Price, M. 39.60.

COMPLETE in detail, well-written, pleasing in type and form, the new edition of this book should be well received by those who are interested in tropical medicine and who read German. Particularly well done are the sections on tropical hygiene and on the prevalence and manifestations of the "cosmopolitan" diseases in the tropics. The illustrations are profuse and as good as any the Reviewer has ever seen in such a work. R. K.

BOOKS RECEIVED.

NEW BOOKS.

*Clio Medica. Vol. IV. Internal Medicine.** By SIR HUMPHRY ROLLESTON, BART., G.C.V.O., K.C.B., M.D., HON. D.Sc., D.C.L., LL.D. Pp. 92. New York: Paul B. Hoeber, Inc., 1930. Price, \$1.50.

*A Text-book of Histology.** By ALEXANDER A. MAXIMOW. Completed and edited by WILLIAM BLOOM. Pp. 833; 604 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$9.00.

Report on Fifth International Congress of Military Medicine and Pharmacy, London, England, May, 1929. By COMMANDER WILLIAM SEAMAN BAINBRIDGE, M.C.-F. Pp. 154; 23 illustrations. Menasha, Wis.: George Banta Publishing Company.

The British Journal of Psychology, Monograph Supplement XIV; The Subjective Character of Cognition. By R. B. CATTELL, B.Sc., Ph.D. Pp. 166. Cambridge: University Press, 1930. Price, 12s 6d.

Collected Publications from the Robert Dawson Evans Memorial for Clinical Research and Preventative Medicine, No. 1, Endocrine Studies, 1929.

*Medicine in Virginia in the Seventeenth Century.** By WYNDHAM B. BLANTON, M.D. Pp. 337; illustrated. Richmond: The William Byrd Press, Inc., 1930.

*Medicine Monographs, Vol. XVII. Ephedrine and Related Substances.** By K. K. CHEN and CARL F. SCHMIDT. Pp. 121. Baltimore: The Williams & Wilkins Company, 1930.

* Reviews of titles followed by an asterisk will appear in a later number.

- Monograph No. 23 (August 15, 1930) of the Rockefeller Institute for Medical Research: The Treatment of Human Trypanosomiasis with Tryparsamide. A Critical Review.* By LOUISE PEARCE, M.D. Pp. 339. New York: The Rockefeller Institute for Medical Research, 1930.
- The Pathology of Diabetes Mellitus.** By SHIELDS WARREN, M.D., with a Foreword by ELLIOTT P. JOSLIN, M.D. Pp. 212; 85 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$3.75.
- Pernicious Anemia.** By LEYBOURNE STANLEY PATRICK DAVIDSON, B.A. (CAMB.), M.D., F.R.C.P.E., and GEORGE LOVELL GUILLAND, C.M.G., LL.D., M.D., F.R.C.P.E. Pp. 203; 30 illustrations. St. Louis: The C. V. Mosby Company, 1930. Price, \$8.50.
- Ueber die akute und chronische gelbe Leberatrophie.** By PROF. DR. HILDING BERGSTRAND. Pp. 118; 68 illustrations. Verlag, Leipzig: Georg Thieme, 1930. Price, M. 14.
- Progressive Medicine, Vol. III. September, 1930.* Edited by HOBART AMORY HARE, M.D., LL.D., assisted by LEIGHTON F. APPLEMAN, M.D. Pp. 327. Philadelphia: Lea & Febiger, 1930.
- Diseases of the Skin** By GEORGE CLINTON ANDREWS, A.B., M.D. Pp. 1091; 988 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$12.00.
- Aphasia in Children.** By ALEX. W. G. EWING, M.A., PH.D., with an introduction by E. D. ADRIAN, M.D., F.R.C.P., F.R.S. Pp. 152. New York: Oxford University Press, 1930. Price, \$3.50.
- Dosage Tables for Roentgen Therapy.** By PROF. FRIEDRICH VOLTZ, translated from the second German edition. Pp. 120; 21 illustrations. New York: Oxford University Press, 1930. Price, \$2.50.
- Arterial Hypertension.** By EDWARD J. STIEGLITZ, M.S., M.D. Foreword by ROLLIN T. WOODYATT, M.D. Pp. 280; 21 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$5.50.
- Nervous Indigestion.** By WALTER C. ALVAREZ, M.D. Pp. 297. New York: Paul B. Hoeber, Inc., 1930. Price, \$3.75.
- Anatomy of the Human Body.†* By HENRY GRAY, F.R.S. Revised and re-edited by WARREN H. LEWIS, B.S., M.D. Pp. 1391; 1232 illustrations. Twenty-second edition. Philadelphia: Lea & Febiger, 1930. Price \$10.00.

NEW EDITIONS.

- Physiological Chemistry.* By ALBERT P. MATTHEWS, PH.D. Pp. 1233; 109 illustrations. Fifth edition. New York: William Wood & Co., 1930. Price, \$7.00.
- Stedman's Medical Dictionary.* By THOMAS LATHROP STEDMAN, A.M., M.D. Pp. 1222; illustrated. Eleventh revised edition. New York: William Wood & Co., 1930. Price, \$7.50, net.
- The only standard work of its kind with a new edition appearing in 1930. The discussion in the two prefaces of "barbaric" orthography is recommended to those with a taste for etymology, though the author's views are only partly endorsed. The advantage of finger indexes for each letter through the book is not inconsiderable.
- Gonococcal Infection in the Male.* By ABR. L. WOLBARST, M.D. Pp. 297; 140 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$5.50.

* Reviews of titles followed by an asterisk will appear in a later number.

† Review page 712.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Plasma Proteins in Relation to Blood Hydration. V. Serum Proteins and Malnutritional or Cachectic Edema.—BRUCKMAN and PETERS (*J. Clin. Invest.*, 1930, 8, 591) note that experimental reduction of protein intake produces corresponding depletion of serum protein in rats, together with edema, a condition which may be compared to the edema that develops in famine areas and in patients who have wasting disease. They believe that malnutrition, attended by serum albumin deficiency, affords the rational explanation for the development of this particular edema. Their studies indicate that there is no correlation between the occurrence of edema and globulin concentration. Globulin, even in those patients with edema, may be high as well as low. The correlation with serum albumin is better than with total protein. This is as it should be. If the edema depends upon osmotic pressure exerted by the serum proteins, then the importance of albumin should be much greater than globulin because the serum albumin has a much greater influence on osmotic pressure than serum globulin. The edema occurs when serum albumin falls below 3 per cent. This is an invariable finding. It rarely occurs when the albumin exceeds 4 per cent. They conclude that the malnutrition edema is dependent upon serum albumin deficiency through loss of body protein, the result of disease or inadequate diet.

So-called Malignant Hypertension: A Clinical and Morphologic Study.—Malignant hypertension has roused considerable interest the last few years from several points of view, but the essential nature of the disease has stirred up more interest than any other one problem of the disease. MURPHY and GRILL (*Arch. Inter. Med.*, 1930, 46, 75) in a very careful study of 16 patients selected from a total of 629 studied

in a period of four years, present some interesting facts and draw certain conclusions deduced from an analysis of the clinical data, as well as from postmortem findings in 12 patients. This group of patients presented clinically severe headache, marked loss of weight, persistent and extreme hypertension, functional failure of one or more important organs, a progressively rapid downhill course associated with characteristic retinal changes. The important pathologic lesions in all these individuals were arteriosclerotic, a sclerosis which invariably involved the smallest arteries and arterioles. In the media of the arterioles of the skeletal muscles a fairly high degree of hypertrophy was found and this was found occasionally in the arterioles of the kidneys, which organs, incidentally, in 6 cases showed necrotic lesions in the walls of the afferent glomerular arterioles and the loops of the corresponding glomeruli. The authors believe that malignant hypertension differs from benign hypertension in degree only, in the former there being pronounced clinical symptoms with extensive and destructive lesions in the small arteries and arterioles, as contrasted with the benign forms of the disease.

Classification of the Anemias on the Basis of Differences in the Size and Hemoglobin Content of the Red Corpuscles.—WINTROBE (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 1071) made a study of a series of patients, 140 in number, suffering from various types of anemia. He presents a classification of anemia based on the size of the cell and the hemoglobin content of the red corpuscle—an extremely simple classification but one which has greater accuracy than the older subdivision of the anemias. The first group is called the *macrocytic* and includes patients who have anemia, pernicious in type, as well as sprue and pernicious anemia of pregnancy. There is an increase in the size and hemoglobin content of the red cells in these cases. The next group is the *normocytic*, in which corpuscular concentration is normal; that is to say there is a reduction in the total number of red cells, but without notable change in the size or the hemoglobin content of the red cells. In this class is placed those cases of anemia that result from acute hemorrhage, malaria, and anemia of the so-called aplastic type. Type III is the *simple microcytic*, the most frequently observed type of anemia, the secondary anemia of former writers. In this type of anemia, depending upon the severity, there is a more or less marked reduction of volume of the red cell and corpuscular hemoglobin, but at no time is the decrease as great as is the reduction in the number of red cells. This is the type of anemia associated with chronic infections, malignant disease and chronic cardiovascular or renal disease. The fourth type of microcytic anemia is the *hypochromic*, observed chiefly as a result of chronic blood-loss and notably in cases of uncinariasis. In this type of anemia there is a distinct reduction in the volume of the red cells and a considerable decrease in the hemoglobin content. The lowest values for mean corpuscular volume are in this particular division. The mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular concentration are calculated from three known figures: the number of red cells, the quantity of hemoglobin and the relative volume of packed red cells after centrifugation.

The Metabolism of Normal and Leukemic Leukocytes.—Leukocytes are able to transform dextrose into lactic acid while they also use a considerable quantity of oxygen. In normal blood the erythrocytes far outnumber the leukocytes and the sugar consumption is due in part to these former cells, but if the total white count is markedly increased, as in leukemia, the consumption of sugar is increased markedly as a result of leukocytic metabolism. GLOVER, DELAND and SCHMITZ (*Arch. Int. Med.*, 1930, 46, 46) undertook an investigation to determine if the metabolism of white cells bears a relationship to the maturity of the cells and to find out if the metabolism of leukemic white cells is in any way different from the normal cells, as the metabolism of cancer tissue differs from normal tissue. Thus it might be possible to secure some information as to the possibility of leukemia being essentially a malignant disease. Without discussing the technique they employed, suffice it to say that as a result of the work, it has been shown that the metabolism of the white cell of the leukemic blood varies according to the degree of maturity: the greater the oxygen consumption, the more mature the cells; the smaller the sugar consumption, the more mature the cells. Normal white cells are more active than leukemic white cells in consuming oxygen and sugar. Sugar consumption in the normal leukocyte and mature myelogenous cell resembles cancer tissue, whereas the immature myelocyte and both mature and immature lymphocyte cell utilize sugar much as does embryonic tissue.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

Embryology, Anatomy and Surgery of the Prostate Gland.—LOWSLEY (*Am. J. Surg.*, 1930, 8, 526) says that it is concluded from a large series of cases (373) that the most important item in the care of a case suffering from prostatic disease is suitable drainage until the patient reaches the maximum of renal efficiency. The best preliminary drainage is the suprapubic double suction, because it diminishes the edema of the prostate and thus is a factor in reducing bleeding. Sacral or parasacral is the most suitable anesthesia for prostatectomy. Its advantages are: (a) It is efficient; (b) it allows the patient to take fluids up too, during and immediately after operation; (c) the bleeding is very much less than it is with any other kind of general anesthesia; (d) anesthesia persists for several hours after operation making the administration of morphia with its attendant bowel stasis unnecessary in many instances. Perineal prostatectomy is preferred because there does not seem to be so much shock as noted in the suprapubic operation. The postoperative drainage is accomplished by means of an urethral catheter which allows both the perineal and the suprapubic wounds

to close. The average postoperative stay in the hospital has been reduced to twenty-two and seventy-six hundredths days. Almost 10 per cent of the prostates operated on were carcinomatous. The mortality for the adenomatous cases was 5.7 per cent while there were 3 deaths out of 33 cases of carcinoma.

The Incidence of Allergy and Asthma in a Group Developing Postoperative Atelectasis.—WILMER, COBE and LEE (*Ann. Surg.*, vol. 91, p. 651), from their study report that 10 cases of postoperative massive atelectasis have been followed and an analysis of their histories and careful testing has shown all 10 of them to be definitely allergic. In all cases the consistency of the sputum has been described as viscid, tenacious and purulent, and apparently similar in its physical properties to the bronchial secretion so characteristic in all allergic individuals manifesting respiratory symptoms. In the positive cutaneous tests they found 5 reacting to pollen; 2 to animal emanation; 2 to bacteria, and 1 with eczema probably had a food sensitivity. In listing the results of the tests the major reactor was the only one recorded, but most of the cases reacted to more than one protein. The surprising incidence of asthma and allergy found in this small group of patients who developed postoperative atelectasis, suggests another etiologic factor that should be considered in the study of this phenomenon.

The Cause of Death in Uncomplicated High Intestinal Obstruction.—WHITE and FENDER (*Arch. Surg.*, 1930, 20, 897) say that a dog with complete high intestinal obstruction was kept alive and in good condition for a month. This was accomplished by preventing the loss of its digestive secretions, these being immediately reinjected into the lower unobstructed bowel. It is extremely unlikely that any potent toxin formed in the obstructed intestine can be absorbed by the mucous membrane as long as its blood supply is maintained; otherwise, life would have been shortened rather than prolonged by the reinjection of the obstructed secretions. The theory of the beneficial effects of salt solution is due to the neutralization of the toxin by the chlorid radical seems illogical. This animal received no salt from outside sources and become considerably dechlorinated during the prolonged obstruction owing to a small, unavoidable daily loss. The dechlorination of the tissues corresponded to that of the blood. As the nonprotein nitrogen and nitrogen output in the urine remained normal, there is no evidence that tissue protein was destroyed by toxin. The authors believe that death in the uncomplicated high obstructions is due mainly to loss of salt and water, possibly also to other substances, in the gastrointestinal secretions. When inorganic electrolytes are lost rapidly and are not replaced it becomes impossible for the organism to retain its normal water content. This leads to changes in the physico-chemical equilibrium of the blood and tissues.

Traumatic Pneumocephalus.—RAND (*Arch. Surg.*, 1930, 20, 935) says that traumatic pneumocephalus may be broadly used to designate the entrance of air into the brain or cranial cavity following a fracture of the skull. Any case of fracture of the skull communicating with an accessory sinus, particularly the frontal, should be closely watched for

the possible development of pneumocephalus. This complication may appear at once or more often several weeks after the injury. The presence of cerebrospinal rhinorrhea should increase precautionary measures. The patient should be cautioned against sneezing, coughing or any action that may intensify the air pressure in the accessory nasal sinuses. If pneumocephalus is demonstrated, whether the air is present in the frontal lobe, lateral ventricles or both, its removal should be attempted at once, together with closure of the dural rent. Signs of meningitis are often present, even in the absence of infecting organisms; consequently they should not necessarily deter an attempt to correct the pneumocephalus. It may even be justifiable to proceed in certain cases in which infecting organisms have been demonstrated in the fluid. The prognosis in cases of pneumocephalus is probably better if operative rather than expectant treatment is used. Success depends largely on early and prompt intervention.

Kidney and Ureteral Lesions Secondary to Adnexal Disease.—VON LICHTENBERG (*J. Urol.*, 1930, 24, 1) claims that a large number of kidney region symptoms in males have adnexal disease as the etiologic factor. A number of cases of ureteral strictures, ureteral kinks, periureteritis, perinephritis and of pyogenic kidney diseases are caused by diseases of the adnexa. A viewpoint of system pathology leads to a correct diagnosis in such cases and forms the background for proper treatment. A viewpoint of system pathology allows the correct pathologic evaluation of ureteral disease. By this means we find the connecting link which joins the diseases of the lower urinary tract and genital organs with those of the kidney into one pathologic and clinical unit.

Stenosing Tendovaginitis at the Radial Styloid Process.—FINKELSTEIN (*J. Bone and Joint Surg.*, 1930, 12, 509) declared that in 1895 De Quervain described a previously unrecognized condition affecting the tendon sheath of the abductor longus and extensor brevis pollicis tendons, which occupies the first compartment on the dorsal surface of the radius near the styloid process. This disease is frequently encountered, 24 cases being operated upon in a single institution within a period of two years. The laboring classes are most frequently affected. Chronic trauma and overexertion are the most common causes. The disease can be produced experimentally. The pathologic changes are usually limited to a fibrous thickening of the tendon sheath, without evidences of acute inflammatory reaction. There may finally occur calcareous deposits in the sheath. In rare instances, however, the lesion may occur in the tendon itself and often there are distinct evidences of inflammatory reactions in the peritendinous structures. The pain over the styloid process of the radius may be excruciating, causing disability and interfering with the pursuit of a livelihood. The disease is progressive; it is amenable, except in rare instances, to conservative treatment after four weeks' duration; but responds readily to operative intervention, which consists of splitting the stenosed tendon sheath or in severe cases, the entire removal of the tendon sheath.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

The Treatment of Hypochromatic Anemia With Large Doses of Reduced Iron.—SCHULTEN (*München. med. Wchnschr.*, 1930, 77, 355) tested the effect of the administration of large amounts of iron on patients who, following loss of blood, during a control period of three to four weeks showed no appreciable tendency to blood regeneration. After various doses had been tested, the administration of daily doses of 6 gm. of ferrum rednetum, in 30 equally divided pills distributed over twenty-four hours, was applied. This relatively large dose was well tolerated by the patients. Untoward manifestations were observed only occasionally in patients with duodenal ulcer, but a number of patients, even in the presence of the ulcer, tolerated the iron well. The effect of such large doses of iron was often surprisingly good. The reticulocytes may show a rise as early as one to three days after the beginning of treatment. This increase of reticulocytes is followed by a rise in the erythrocytes and hemoglobin. The average daily rise in the hemoglobin was from 2 to 3 per cent. Patients were observed who did not respond beneficially to the daily administration of 2 gm. of reduced iron, who nevertheless responded promptly to the daily administration of 6 gm. In addition to the cases with anemia due to loss of blood, the author observed similar beneficial effects after the administration of large doses of iron in patients suffering from "chloranemia with achylia." Patients having this disease exhibit an hypochromatic blood picture—achylia gastrica and absent increased hemolysis. Hematin and bilirubin cannot be detected in the serum. The urobilin and urobilinogen are not increased in the urine or stool. This anemia does not respond to the administration of liver. In this condition the administration of large doses of iron is especially important. One case is quoted in which the anemia improved only when the dose of iron was raised to 9 gm. daily. The exact mechanism through which the iron exerts its beneficial effect is unknown to the author.

The Treatment of Abscess and Gangrene of the Lung.—In view of the conflicting opinions as to the rational treatment of abscess of the lung, NEUMANN reports (*Wien. klin. Wchnschr.*, 1930, 43, 261) his experiences in the Wilhelminen Hospital of Vienna. The routine treatment in this clinic starts with the intravenous injection of neosalvarsan. If within eight to ten days there is a decrease in the fever,

and a disappearance of the foul-smelling sputum, this treatment is continued until the evidence of abscess disappears even on the Roentgen ray picture. Of the 13 patients treated in this manner, 5 recovered completely, 7 improved to the extent that the fever and the foul sputum disappeared, but the Roentgen ray picture continued to show infiltration. One case with bilateral abscess died on the second day of treatment, hence this case should be excluded from the series. If, after the elapse of eight days, the fever and expectoration are unchanged, pneumothorax is induced and the injection of neosalvarsan continued. Of the 13 cases treated in this way, 7 left the clinic as cured, 4 as improved and 2 died. While pneumothorax in these cases was beneficial, its application in this condition is not without danger, particularly if the location of the abscess is near the pleural surface. In such cases the abscess may break into the pleural cavity, a complication usually leading to a highly toxic condition because of the great absorptive capacity of the pleural surface. In case of rupture of the abscess into the pleural cavity, immediate surgical drainage of the pleura is essential. Only in cases in which pneumothorax is not applicable, either because of adhesions or incomplete collapse of the cavity, is surgical operation indicated. Of the 6 cases treated surgically, 4 were cured and 2 died.

The Action of Large Doses of Vitamins in Experimental Infection.—PFANNENSTEIL and SCHARLAU (*München. med. Wchnschr.*, 1930, 77, 619) report the results of a series of about 200 carefully controlled experiments in which they sought to determine whether or not the use of fairly large doses of vitamins, singly or in combination, was capable of influencing the course of experimental infections in animals. They tested these agents upon rabbits infected by tubercle bacilli of known virulence, upon rabbits similarly infected after previous partial immunization and upon skin infections in rabbits produced by the injection of hemolytic staphylococci. The vitamins employed were D, as represented in irradiated ergosterol; B, as obtained in dried yeast or yeast extract and A as obtained in cod-liver oil. The results of these experiments showed that the administration of relatively small doses of ergosterol with large doses of dried yeast exercised marked therapeutic action, shortening the course of the infection, promoting healing and, in the case of tuberculosis, preventing spread of the disease. The combination of vitamin D with calcium and to a lesser extent the administration of vitamin D alone notably diminished the inflammatory reaction following the inoculation of staphylococci. On the other hand, vitamin B and vitamin A promoted the healing process although it had no influence in diminishing the local inflammatory reaction. Suggestive results have been obtained by the authors in a few instances in which they have applied the same methods of vitamin therapy in man.

Experiences With the Treatment of Graves' Disease by the Injection of Animal Blood.—This form of treatment, published by Bier in 1929, has recently been investigated in a series of 18 carefully controlled patients by His (*Deutsch. med. Wchnschr.*, 1930, 56, 606). He controlled the results by weight, pulse rate, basal metabolism and other similar objective data. He endeavored to follow Bier's technique pre-

cisely, even obtaining the fresh blood in many instances from Bier's own clinic. The bloods used were sheep's blood and beef blood; the dose was 5 cc. and the number of injections 2 to 5. He concludes, from this study, that control of the disease, or even merely a significant improvement in the symptoms, was not produced in a single patient. One patient did show a fall in the basal metabolism but this took place before the treatment had gotten well under way, and was paralleled by similar spontaneous falls observed in the control period in other patients.

New Results in Diphtheria Prophylaxis.—Pointing out the demonstrated inherent dangers from the injection of toxin-antitoxin which seem to be, in part, absolutely unavoidable and calling attention to the comparative unsuitability of the injection method for large scale immunization, LÖWENSTEIN (*München. med. Wchnschr.*, 1930, 77, 883) reports the extensive experience of himself and his associates with his inunction method. The technique consists in cleaning the skin of the back or chest with soap and water, or ether, followed by inunction with the moistened hand of diphtheria bacillus salve for a period of three minutes. This inunction is repeated twice at intervals of fourteen days. No reaction is produced, no harmful effects have been seen and there are no contraindications to this form of prophylaxis. After four or five days there is a fairly high degree of immunity present in the patients. Negative Schick reactions are obtained by this form of immunization in approximately 80 per cent of patients. More than 60,000 inunctions have been given. In several small groups of children perfectly controlled in institutions, this technique has promptly reduced the incidence of diphtheria to 0 in the face of rising diphtheria incidence in the general child population at large.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Subdural Hemorrhage Associated with Tentorial Splitting in the Newborn.—CHASE (*Surg., Gynec. and Obst.*, 1930, 51, 31) studied 32 cases and he feels that subdural hemorrhage is the important intracranial lesion in most cases of birth trauma. He found nothing to indicate that intradural hemorrhage or tentorial splits were of themselves worthy of clinical significance. The subdural hemorrhage is largely supratentorial and often bilateral. It is usually caused by stretching and rupturing of the small tributaries of the great cerebral vein near its junction with the straight sinus. Tentorial splits are relatively more numerous in the premature than in the full-term baby, partly because of the greater immaturity of the fibers of the dural septums in prematurity. The causes of prolonged and difficult labor may be as important factors in these intracranial as operative inter-

vention. Signs of asphyxiation were constant in this series, but definite signs of intracranial irritation were recorded in only a small minority of the cases.

Diabetes Mellitus in Children: Malformations.—PRIESEL and WAGNER (*Ztschr. f. Kinderh.*, 1930, 49, 419) report the malformations found in a study of 107 diabetic children. In the same family there was one case of gigantism and one case of dwarfism. In one child there was a fusion of the posterior portion of two ribs with the result that the adjacent intercostal spaces were abnormally wide. In another child the sternal end of the osseous portion of one of the ribs was enlarged. One child had a curvature of the little finger resembling the condition that occurs in Mongolian idiocy, except for the absence of curvature of the middle phalanx. In a large number of the children scaphoid scapulæ were seen. In some of the children, hyperextensibility of the joints was noted. In one case this condition was present in a child who also had a subcutaneous nodule in one of his ears and an accessory nipple. Other malformations noted were one case of congenital luxation of the patella, one of marked lordosis with definite lordotic albuminuria, one of congenital cataract, one of Dupuytren's contracture, one of inguinal hernia on the right side and a patent inguinal canal on the left, one of defects on the distal end of the incisors, one of concurrence of ichthyosis with a large pigmented nevus below the right nipple, one of concurrence of unilateral congenital hypermetropia and congenital absence of the uvula, one of infantilism, one of premature hyperplasia and pendency of the mammary gland, and one of imbecility. The authors feel that some of the stigmata that occur in diabetic children are not discovered until an exact examination is made of the slightest deviations from the normal.

The Insensible Perspiration in Infancy and in Childhood.—LEVINE and MARPLES (*Am. J. Dis. Child.*, 1930, 40, 269) made a statistical study of the available data on the basal metabolism and basal insensible perspiration of normal infants. They made a similar study of a statistical and experimental nature of the correlation between the two variables in simultaneous calorimetric measurements as well as in independent measurements with the respiration chamber and balance, respectively. Their results verify by statistical methods, the validity of the tentative standards recently proposed by the authors for the basal insensible perspiration of normal infants and indicate that they compare favorably in reliability with the generally accepted standards for the basal metabolism of these subjects. The evidence also establishes a high positive correlation between the physiologic mechanisms of heat production and insensible perspiration in the human subject, whether measured simultaneously in the respiration chamber or independently with the balance and respiration chamber. The evidence of correlation between the two variables in independent measurements is as yet limited to infants and adults. The demonstration of casual relationship in infants between the two mechanisms was used to extend to these subjects the method proposed by Benedict and Root for pre-

dicting the probable metabolism of adults from their insensible perspiration measured with a balance. This method gave satisfactory results in the small number of infants so far studied. Among these there were several subjects with an abnormal respiratory exchange. The proposed method of prediction is at present limited to infants studied under basal conditions, but it is probably applicable to other than basal conditions so long as visible perspiration is not present and in absence of derangement of water metabolism. The authors have used this method clinically and recommend it for clinical use.

Nutrition of Children on a Mixed and on a Vegetable Diet.—LANE and BOSSHARDT (*Am. J. Dis. Child.*, 1930; 40, 285) conclude from their observations that there is no reason that a scientifically balanced milk diet, including $1\frac{1}{2}$ pints to 1 quart of milk per day per child should be expected to produce greater growth or better health in growing children from seven to fifteen years of age than a scientifically chosen vegetable diet furnishing a smaller amount of calcium. If there is a greater storage of calcium on the milk diet than on the vegetable diet, a supposition which did not seem to be justified by the gains in weight and height or the other data gathered by the observers, there still would seem to be no reason for assuming that such excessive storage was advantageous for the general health of growing children. Excessive calcium storage may possibly obscure a clear perception of the function of other factors in the diet, whether it be that of the calorie-producing nutrients, the various minerals and vitamins or the acid-base equilibrium of the blood. A diet of vegetables carefully selected with special attention to the quality and quantity of the protein, low in fat, comparatively high in carbohydrate, with adequate amounts of the various minerals and high in vitamins produced in a period of ten weeks as satisfactory increase in all the physical measurements as those observed in children from seven to fifteen years on a similarly carefully planned milk and meat-containing diet. In most cases the increases were greater.

Conditions Simulating Thymus Disease and Their Diagnosis.—HIGGINS (*Penna. Med. J.*, 1930, 33, 866) points out some of the conditions from which thymus disease must be differentiated. He groups these under two headings the first comprising conditions seen in the newborn and the second, those seen in older infants and children in general. In the first group he enumerates excessive mucus in the respiratory passages; intracranial hemorrhage; atelectasis; enlarged thyroid; congenital heart defect; congenital stridor; congenital defects of the respiratory passages; and sepsis. In the second group he includes spasmodic croup; laryngismus stridulus; foreign body; laryngeal diphtheria; spasmodic croup; acute laryngitis; mediastinal tumor; enlarged bronchial glands; retropharyngeal abscess; whooping-cough; bronchopneumonia; nasal polyps; and petit mal. He emphasizes the value of the Roentgen ray in clearing up the diagnosis. In selected doubtful cases he urges the therapeutic test of radiation therapy, which does so much good in thymus cases and in properly controlled doses is very unlikely to cause any harm in cases that are not thymic in origin.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Epidermophytosis of the Feet and Epidermophytids of the Hands.

—PECK (*Arch. Dermat. and Syph.*, 1930, 22, 40) discusses the pathogenesis of the dyshidrotic (vesicular) and squamous eruptions on the hands which so often accompany proved mycotic infection of the feet. Fifty cases from Bloch's Dermatologic Clinic in Zurich showing this clinical association of hand and foot lesions were subjected to microscopic and cultural studies of scrapings made from the involved sites. In 48, fungi were demonstrated easily and in great numbers from the lesions on the feet, while in the same patients the dermatitic patches on the hands were negative for fungi. Only 2 patients in the series gave positive results from both the hands and feet. The author refuses to accept Sabouraud's contention that the negative results from hand scrapings are due to technical difficulties and seeks for a further explanation of the phenomenon. He points out that von Graffeuried was the first to show that in spite of the apparent superficiality of the foot infections, an allergic state is produced with a positive trichophylin reaction. Furthermore, the name trichophytid (epidermophytid or dermatophytid) has been given to the mycotic eruption which develops when a fungous element (or toxin?) is hematogenously transported from the site of a primary fungous infection to the allergic skin. From a previous study by Jadassohn and Peck and the writings of Williams, Bloch and others the author points out that this conception of "phytid" best explains the relationship between the associated hand and foot lesions. The fact that an occasional patient shows a positive scraping from the secondary hand lesion is attributed to early examination before the allergic state of the skin has destroyed all of the fungous elements transported from the primary focus. The present paper reports on (1) the clinical investigations of 23 new cases of foot mycosis combined with pathologic changes on the hands; (2) histologic examination from both sites; (3) cultural and microscopic studies of the fungi isolated; (4) a positive blood culture for fungi and (5) the experimental reproduction of epidermophytosis and epidermophytid. In summarizing these data the author notes that the secondary manifestation on the hands usually appears some time after the foot mycosis has been established and not infrequently after the latter has been subjected to mechanical or chemical trauma (treatment). The lesions on the hands do not usually clear until the primary mycosis is properly treated.

Histologically there is no difference between the primary mycotic lesion and its secondary expression except for the absence of fungi in the latter. A single case in which a positive blood culture for epidermophyton Kaufmann-Wolf was obtained is presented in detail as well as a case dealing with the first experimental production of the syndrome in a previously well human being. These 2 cases materially help to establish the truth of the epidermophytid theory.

The Use of Solution of Pituitary in Herpes Zoster.—SIDLICK (*Arch. Dermat. and Syph.*, 1930, 22, 91) following the suggestion of Vandell has treated 54 patients with herpes zoster by the intramuscular administration of obstetrical pituitrin in doses varying from 0.5 to 1 cc. The number and frequency of treatments depends on the intensity of the pain but averages two doses, given a day apart. The author stresses the effectiveness of the method in controlling pain and the rapidity with which the cutaneous lesions disappear. Pregnancy is the only known contraindication to the treatment.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Calcium Therapy of Adnexitis.—So many remedies have been claimed to be of value in the treatment of salpingitis, particularly in the literature of Central Europe, that a reviewer becomes quite skeptical of them all, especially in a condition of this sort in which the element of time alone is all that many of the cases require. However, an enthusiastic report on the use of calcium injections as a means of combating the symptoms of pelvic inflammatory disease which has been presented by BOESKEN (*Zentralbl. f. Gynäk.*, 1930, 54, 733) temporarily arrests our attention. He admits that in the treatment of chronic inflammation of the tubes, the results from this form of therapy are not greatly superior to the other methods of conservative treatment now in use. In the treatment of acute inflammations however, the results of calcium injection have been unusually satisfactory. The best results have been noted in the highly acute cases, especially in the beginning of the attack, in which a smooth convalescence was noted in two-thirds of the cases, with improvement in the remaining third. As a rule the first injection is followed by a sharp fall in temperature with coincident cessation of pain and the massive palpable lesions rapidly disappear. At first there was some difficulty from the large amount of calcium which was injected

but now he uses only calcium gluconate, which causes no inflammatory reaction when injected intramuscularly or intravenously. The preparation which he uses is "Calcium-Sandoz" and it is given in 10 cc. doses daily.

Pelvic Actinomycosis.—In this country we give very little thought to the possibility of pelvic inflammatory disease having as its origin the infection by the ray fungus or Actinomyces. In Germany however, reference is often made to this type of infection, which is quite destructive in its progress, having almost malignant characteristics. In describing lesions of this type, SCHUGT (*Münch. med. Wchschr.*, 1930, 77, 394) states that it should be suspected in those cases which are progressive in spite of the usual methods of treatment for the ordinary type of pelvic inflammatory disease. The diagnosis can be clinched by bacterial study of the pus but often the smear may be negative. The prognosis is nearly always unfavorable, although if the diagnosis is made early, surgical treatment may be satisfactory. Of the nonsurgical types of treatment we may try the use of potassium iodid by mouth and the local application of tincture of iodine, copper sulphate or bichlorid of mercury, while occasionally irradiation by means of the Roentgen ray has proved effective. Whereas this condition is by no means a common one, it is a good plan to consider it in the differential diagnosis in all of those cases of pelvic inflammatory disease which prove quite resistant to treatment.

Results of Irradiation in Cervical Cancer.—BOWING and FRICKE (*Radiology*, 1930, 14, 211) have reviewed the cases of carcinoma of the cervix treated with radium at the Mayo Clinic during the years 1915 to 1924 inclusive. The total number of patients treated was 1094 and of these 1001 (91.5 per cent) have been traced. Of the traced cases the five-year cures compose 75 per cent of the operable group, 61.53 per cent of the borderline group, 21.49 per cent of the inoperable group and 24.82 per cent of the modified group. The modified group includes all cases in which the lesions were modified by previous treatment before entering the clinic, such treatment including operation, cautery, radium, Roentgen ray, or other means. Of the 625 cases (57 per cent of all cases) in which microscopic examinations of the growths were performed, epitheliomas were found in 574 (91.84 per cent), adenocarcinomas in 44 (7.04 per cent) and mixtures of the two in 7 (1.12 per cent). Lesions graded 3 and 4 totaled 476 cases (76.16 per cent), 94 (15.04 per cent) were of grades 1 and 2 and 55 (8.8 per cent) were not graded. In this series patients with adenocarcinoma (of all four grades) appear to have had a better rate of survival than those with epithelioma. Patients with epithelioma graded 3 and 4 had a slightly better rate of survival than those with epithelioma graded 2, except for the results after five years among the modified cases.

Diverticula of the Bladder in Women.—In describing the findings in 4 cases of vesical diverticula in women, CRANE (*California and West. Med.*, 1930, 33, 572) calls attention to the rarity of this lesion in the female, comprising about 5 per cent of all cases. He found that there is no definite symptom which would indicate the presence of a diver-

ticulum although bladder tenesmus as demonstrated by severe excruciating pain during and just following urination is the most common symptom. Some emphasis may be placed on the inability of the patient to empty the bladder at one sitting. Most diverticula are symptomless until infection occurs, due to poor drainage in the diverticulum itself or at the bladder neck. Thus the symptoms of a diverticulum are similar to those of an infected bladder or of a bladder-neck obstruction where a stone is present. Such symptoms will usually indicate the need for a cystoscopic examination, which will usually reveal the presence of a diverticulum, but that alone cannot tell the whole story. An opaque catheter curled in a diverticulum, a cystogram and a contrast cystogram taken in more than one plane will give an accurate idea of the size, exact location, number and whether or not free drainage is likely. In regard to the treatment of this condition, the consensus of opinion is to relieve the causative obstruction, whether in the urethra or at the bladder neck, before or at the time of doing the diverticulectomy. This is essential if recurrence of the condition is to be avoided, but excision of the diverticulum is not always necessary if it drains well after relief of the causative obstruction.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

The Argyll-Robertson Phenomenon.—SPILLER (*Arch. Neurol. and Psychiat.*, 1930, 24, 566) refers to an error in the usual definition of the Argyll-Robertson pupil, usually given as a condition in which the pupil does not respond to light but does respond to accommodation and convergence. This definition assumes that the pupillary reflex to light stimulation is entirely absent whereas an impaired or abortive reflex must precede the total absence of the reflex unless the symptoms occur suddenly. The abortive or impaired reflex has exactly the same clinical significance and is generally regarded as an Argyll-Robertson pupillary reflex phenomenon. The interpretation of the reflex phenomenon must be influenced by the manner in which the test is made. The source of light must be known, that is, whether daylight or electric or other light, and whether a strong or weak light was used. Disturbance of vision from opacities in the media, optic neuritis, choked disk, or retinal disease must be eliminated. Two sets of fibers, the so-called "pupillary fibers" of Gudden and the visual fibers are involved in the Argyll-Robertson reflex. When the pupillary fibers which are thought to be more resistant than the visual fibers are affected the light reflex in case of progressive atrophy is impaired but not lost until the atrophy is complete. The pupillary fibers may be damaged anywhere along the optic nerve or optic tract, so that not all cases of Argyll-Robertson pupil signify a gross lesion in the corpora quadrigemina. The author's

case was a woman who apparently had tabes. Unilateral Argyll-Robertson pupil on the left side with a normal pupil and adequate reflex movements on the other side was observed. Vision was 5/5 in each eye. The lesion was evidently in the center of pupillary innervation of the left eye as there was no lesion in the visual pathways. "The case is clinical proof that there must be a center in the oculomotor nucleus of each side that is concerned with the function of pupillary action on the same side. Such a center is supposed to be the Westphal-Edinger nucleus."

The Diagnostic Problem in Orbital Cellulitis.—BABBITT (*Ann. Otol., Rhinol. and Laryngol.*, 1930, 39, 444) described 4 cases of orbital cellulitis in which cavernous sinus thrombosis was suspected but not proven. The modern conception of orbital cellulitis excludes the idiopathic and metastatic views and recognizes septic thrombophlebitis, focal infection, and direct extension from the paranasal sinuses. The thickened walls and hyperplastic membrane of the sinuses as shown by roentgenography, as well as the findings by pharyngoscopy lend considerable aid in diagnosis of obscure sinus disease as the source of the cellulitis. The mode of entrance of infection of the orbit from the sinuses includes extension of inflammatory processes through bone, by way of periostitis, through dehiscences in bony walls or by extension by thrombosis of one of the large veins perforating bone and spreading infectious material to the other side. The position of the cavernous sinus with relation to surrounding structures renders it vulnerable to extension of inflammatory processes about the sinus and orbit. The symptoms of acute orbital cellulitis and cavernous sinus thrombosis are so much the same that the decision between orbital abscess and cavernous sinus involvement complicates the simple problem of extension. A comparison of the symptoms of orbital cellulitis and cavernous sinus thrombosis as given by various authors show that exophthalmos, and extension to the other eye, occurs in both. It is difficult to separate the ptosis of paralysis from that of inflammatory edema, rigid position of the eyeball due to paralysis of the third, fourth, sixth nerves from the fixation due to engorgement of adjacent tissue. Intraocular changes, pain and its reference, failure in vision, symptoms of toxemia or profound sepsis and laboratory blood studies are relatively alike, with the possible exception of high leukocyte count and blood-stream infection. He concludes that so-called orbital cellulitis is a secondary manifestation of infection and is a symptom complex rather than an entity, and is due to nasal sinus disease save in cases of obvious external cause. The low percentage of recovery under radical procedure and the serious prognosis without interference justifies initial sinus surgery, even in cases of doubt.

Orbital Cellulitis in Children.—SMITH (*Brit. Med. J.*, July, 1930, No. 3626, p. 14) emphasizes the importance of proptosis when associated with inflammation and attempts to make clear the difference in signs and symptoms of the two main types of orbital cellulitis and the difference in outlook and treatment which each demands. Orbital cellulitis in children has three chief causes: (1) Skin infections, such as

impetigo, hordeolum, fly bites, boils, or any facial wound, with accidentally superadded virulent infection. The temperature is generally very high; septic cavernous sinus thrombosis and general septicemia with pneumonia are likely to supervene, and they often end fatally and rapidly. (2) Nasal sinus infection the commonest cause, is usually not so severe. The eye is pushed outward as well as forward. This is a strong diagnostic point. The ethmoid cells or antrums should be opened. Early operation is desirable. (3) Osteomyelitis or periostitis of the orbit is a rare but important cause. Edema and chemosis may occur from osteomyelitis of the rim of the orbit outside the orbital fascia. As more than 60 per cent of the cases of orbital cellulitis are of nasal origin, a rhinologist should be consulted early and surgical exploration of the sinuses employed. Destruction of the globe can best be prevented by early drainage of the orbit if relief is not secured by operation on the sinuses.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

Modern Aspect of the Anatomy of Tonsils in Relation to Germinal Centers and Lymphocytes.—HEIBERG'S (*Folia oto-laryng.*, 1930, 19, 209) histopathologic study of the tonsils removed at operation from 100 patients revealed similar cellular responses in the pharyngeal and faucial tonsils. Especial attention was focussed on the germinal centers of the lymphoid follicles. These were regarded as centers of phagocytic activity inasmuch as they appeared to destroy many of the lymphocytes produced in the peripheral zones of the follicle. Being larger in healthy persons, these germinal centers were construed as having some relationship to metabolism. Defective centers were surrounded by a wider lymphocytic zone than normal ones. After indicating morphologic characteristics of the lymphocytes, the author states that, as the structural changes apparently were dependent upon the degree of involvement, tonsillar microscopy can be used as an index to severity of infection and prognosis. The author is of the opinion that the function of the tonsil and its relation with metabolism and immunity need further clarification, and cites Schmidt's observations concerning a tonsillar substance capable of producing leukopenia.¹

RETROSPECTOR'S NOTE.—Russ and Suchanek² also encountered a leukopenia in rabbits inoculated with fresh extracts of human tonsils and adenoids.

¹ Retrospect: *AM. J. MED. SCI.*, 1927, 173, 146.

² Loc. cit., p. 440.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

Hodgkin's Disease with Involvement of Bone and Skeletal Muscles.

—A case of Hodgkin's disease is presented by LOCKWOOD, JOHNSON and NARR (*Radiology*, 1930, 14, 445) in a boy aged fifteen years, whose first symptom was shingles and whose chief complaint on admission was backache. At this time a roentgenogram revealed definite bone destruction in the first 4 lumbar vertebræ, the ilium and the femurs, although six months previously no definite changes in these structures were demonstrable. Biopsy established the diagnosis of Hodgkin's disease. The course was one of increasing severity with bone destruction of the dorsal and lumbar vertebræ, ilium and femurs, and involvement of all lymph nodes, lungs, liver and skeletal muscles. The writers think that shingles has too frequently been reported in Hodgkin's disease to be without significance.

Diverticula of the Esophagus are classified by JENKINSON (*Radiology*, 1930, 14, 508) as (1) pulsion, (2) traction and (3) traction-pulsion. The pulsion type may be congenital, be present at an early age, or may develop during late adult life. Symptoms are usually present, and depend upon the amount of food retained in the sac, leading to dilation of the sac, and pressure. These diverticula are most common at the junction of the pharynx and esophagus. If they are in the lower third of the esophagus, the sac is usually small and points down. They probably occur through a weak spot in the esophagus, possibly where a bloodvessel passes through the muscle. Traction type diverticula are most common in the middle third of the esophagus, following some inflammatory process in the lungs, pleura or mediastinum. The adhesions which follow pull the esophagus outward. The sacs are usually small and the apices point upward. They usually cause no symptoms, unless they harbor food and become dilated. They may develop into the traction-pulsion type and become large, due to pressure. Multiple diverticula of the esophagus are not common, but do occur. The cases the author has seen have been located in the middle third, and range in size from 5 mm. to 3 cm. They usually cause symptoms and he believes are of the pulsion type.

Factors of Error in the Roentgenologic Diagnosis of Diseases of the Colon.—WEBER (*Radiology*, 1930, 15, 460) prefers the opaque enema for examination of the colon. Since fecal material in the bowel may not only make satisfactory study of the colon impossible but also produces

defects resembling those of organic disease, the author routinely requires the patient to take 2 ounces of castor oil the evening before examination and cleanse the bowel with a soapy enema next morning. His examination is roentgenoscopic and the abdomen is freely palpated to separate superimposed loops of bowel in order that all parts of the colon may be studied. If the patient has undue difficulty in retaining the enema, or if spasm is marked and perplexing, he administers 60 drops of the tincture of belladonna divided into 3 equal doses, 2 of which are given two hours apart in the evening and the remaining dose next morning an hour before reexamination. The filling defect is by far the most common roentgenologic manifestation of organic disease of the colon, and is produced by cancer, diverticulitis, tuberculosis, chronic ulcerative colitis, extrinsic lesions, organic stricture and syphilis in about that order of frequency. To distinguish between these diseases the examiner must consider the site and configuration of the defect, the presence or absence of a palpable mass, and the fixation or mobility of the affected portion of the bowel.

Injuries Resulting From Irradiation in Beauty Shops, especially for the removal of superfluous hair, are exemplified in 10 cases reported by HAZEN (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 409). Telangiectases, atrophy and wrinkling of the skin occurred in all cases. Seven women who had facial changes still had some hair in the atrophic and telangiectatic areas; 5 gave a history of deep-boring pains in the jaws and 7 had marked atrophy and recession of the gums.

The Analgesic Effects of Roentgen Rays With Especial Consideration of Bone Metastasis of Cancer.—In the opinion of BORAK (*Radiology*, 1930, 14, 328) the fundamental difference in the analgesic effect of Roentgen rays and pure analgesics lies in the fact that the Roentgen rays can influence solely a pain that has arisen under pathologic conditions. In other words, the Roentgen rays act as an analgesic only when they act therapeutically and only to the extent that they exert healing effects. The bone metastases of cancer are of comparatively slight virulence and the most sensitive of all carcinomas to the Roentgen rays. They do not produce pain until the periosteum or nerve trunks adjacent to the bone become involved. By Roentgen therapy, growth of the bone metastasis is not merely checked, but caused to retrogress or disappear. When the dose is properly adjusted, Roentgen therapy thus has a lasting effect on the pain, suppressing it for at least several years. The author cites cases of bone metastasis in which pain was suppressed, and at necropsy the metastasis, which previously was demonstrable roentgenographically, had completely disappeared.

Lead Therapy.—KNOX (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 304) concludes that colloidal lead has been and will be effective in prolonging the lives of some patients with malignant disease. A rare but occasional permanent cure may be expected. In general a patient should be relatively young, not anemic nor cachectic, nor with extensive metastases in order to undertake the treatment. The morphology of the tumor is not an index of its susceptibility to lead. The use of Roentgen rays and lead have probably more effect on the neoplasm than either used alone. These results, as well as those of others who

have used colloidal lead extensively, justify its use in a few carefully selected cases where adequate resources are available for meeting complications. In the same issue (p. 299) Francis Carter Wood expresses the opinion that the future of lead therapy is still doubtful. That it is very dangerous goes without saying, but Wood has treated some 70 patients without a single death from the lead itself. Unfortunately most patients died from the progress of their disease, though a few patients had their tumors arrested. Many years may be required before a final estimate of the procedure can be offered. Even in its present stage it remains the most important contribution to cancer therapy since the discovery of radiation. Ullmann (p. 306) says that any statistical report he might make on lead therapy would appear very discouraging, but after three years he is still using it as an adjunct to irradiation in patients who are beyond reasonable hope of palliation by other methods. His percentage of failures is thus necessarily large, but as encouragement he has several patients who are apparently well after six months to two years. He prefers large doses to small repeated doses, as the anemia induced disappears more rapidly after the large single dose. Fatty changes in the liver are inevitable, but recovery is apparently prompt. He believes also that his results are better when a thorough course of irradiation was given prior to administering the lead.

A Clinical and Roentgenologic Consideration of Pulmonary Infarction.—Hemorrhagic infarction of the lung is usually the result of embolic occlusion of a branch of the pulmonary artery. Common sources of the emboli are vegetative endocarditis, femoral and uterine thrombosis after childbirth, and thrombotic processes in the prostatic, pelvic and femoral veins after operation. Pulmonary infarcts are rarely single and usually occur in groups of ten to twenty. They are most common in the lower lobes, especially along the sharp margins of the lung and the borders of the interlobar clefts, and are wedge-shaped, with the apex toward the hilus and the base toward the pleura. Fibrinous pleuritis occurs early over the infarcted area and exudates frequently follow. Clinically, in nonfatal pulmonary embolism there is usually an abrupt onset of dyspnea and severe pain in the chest. Fever is not high and is often absent. Leukocytosis is usually found. Hemoptysis is of frequent occurrence and is exceedingly helpful in establishing the diagnosis. In the opinion of KIRKLIN and FAUST (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 265) after reviewing 25 cases observed at The Mayo Clinic, it is very difficult and at times impossible to make a diagnosis of pulmonary infarction from roentgenograms. With the clinical data, however, the nature of the shadows appearing on the films may usually be accurately determined. Infiltration at the bases, especially the right base, associated with thickened pleura, are suggestive, especially if the infiltration is well defined and of triangular shape. Early in the course of infarction, only clouding of the costophrenic angle may be seen. Another favorite site of infarction is the lower portion of the upper lobe of the right lung near the periphery and interlobar cleft. It gives rise to a wedge-shaped shadow such as has been described in the literature. Associated pleuritis is no doubt partly responsible for the shadow seen, and the condition may be confounded with ordinary interlobar pleuritis.

Tuberculous Mediastinitis.—Five cases of tuberculosis occurring in adults in which the disease was predominant in the mediastinum are reported by KORNBLUM and COOPER (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 276). The roentgen examination probably affords the best means of diagnosis although the appearance is not pathognomonic. The characteristic appearance is a widening of the mediastinal shadow with a bulge to one side or the other. The outline tends to be smooth and regular, in contrast to the nodular appearance of lymph-gland enlargements, as in Hodgkin's disease, or the globular appearance of many mediastinal tumors. The trachea may be displaced, and, if present, the displacement is toward the side of greatest involvement, whereas in mediastinal tumors the displacement is usually in the opposite direction. Discovery of a parenchymal tuberculous lesion tends to strengthen suspicion that the mediastinal lesion is also tuberculous, but does not establish the diagnosis, which requires close correlation of all the roentgenologic and clinical data.

Roentgen Diagnosis of Lesions of the Jejunum and Ileum.—RITVO (*Am. J. Roent. and Rad. Therap.*, 1930, 22, 160) discusses numerous conditions which are amenable to roentgenologic demonstration. Usually the examination is carried out after the ingestion of a barium meal. Obstruction, if of marked degree, can often be shown without the meal, the loops of gas-distended bowel, which tend to arrange themselves in parallel columns, being readily visible. By giving barium, if not contraindicated by the exigency of the case, the point of obstruction can be determined with varying accuracy. Hypermotility is shown by emptying of the small bowel in less than six hours. Solitary and multiple diverticula, although difficult to exhibit, can be shown under favorable circumstances. Malpositions and displacements of the small bowel by extrinsic tumors may aid in localizing the latter. Tumors of the pancreas usually displace the jejunum downward; those of the spleen toward the midline. Renal tumors cause a downward and outward displacement. Mesenteric masses may be demonstrated by the fact that no loops of small bowel are visible in portions of the abdomen where they normally should be. Tuberculosis causes irritability with hypermotility and filling defects. Tuberculous peritonitis may occasionally be diagnosed by Roentgen studies of the small bowel, which may reveal adhesions and multiple irregularly scattered narrowings; the intestinal loops tend to form bizarre patterns and are shorter and narrower than usual.

Primary Hemangioma of Bone.—The roentgenologic appearance of hemangioma in bone, according to BUCY and CAPP (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 1) is of two types: (1) In flat bones (that is, skull, scapula, pelvis) sunburst trabeculations of unusual size radiate from a common center and mostly from the plane of the bone. The periosteum may be considerably elevated, but is apparently not broken through. (2) In cylindrical bones the tumor is loculated. These loculations are small with an interspersed fine, fibrillary framework. The cortex is usually destroyed but may extend into the center of the expansive tumor. The periosteum, though expanded remains intact.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Pulmonary Siderosis.—Two cases of pulmonary siderosis were reported by BOHRD (*Arch. Path.*, 1930, 10, 179). One case illustrated the black variety, produced by inhalation of metallic iron dust, and this case terminated with a tuberculous bronchopneumonia which showed a relatively small amount of fibrosis. The second case illustrated the red variety of siderosis due to inhalation of dust-containing compounds of iron, of which the most important is the oxide. In this case the concomitant tuberculosis was of the fibrotic type and confined to the lymph glands. In both varieties transportation of a portion of the iron particles by macrophages was noted. These cells carried the particle into the alveoli and thence into the sputum along with a fraction which was excreted through the bronchial mucosa. Other particles were carried to the neighboring lymph nodes, being either deposited there, or else carried on into the blood stream, probably by way of the thoracic duct. Particles of iron in the blood stream were taken up by cells of the reticulo-endothelial system. A gradual transformation of the iron into a relatively insoluble protein compound was suggested. Only the more soluble iron was found to be capable of transportation and it was found intracellularly, while the insoluble compounds were found extracellularly in dense fibrous tissue.

The Etiology of Lymphadenoma: A Summary of Six Years' Researches.—TWORT (*J. Path. Bact.*, 1930, 33, 539) studied 106 cases which clinically resembled lymphadenoma. They were carefully analyzed and searched for parasites of different kinds. The author found, however, that although a variety of parasitic forms, both animal and vegetable were observed in the tissues, or cultured from them, there was no uniformity in the appearance of any variety. The author admits that the etiology of lymphadenoma (Hodgkin's disease) remains obscure to us.

The Giant Cells of Benign Giant-cell Tumors of Bone.—JOHNSON (*Arch. Path.*, 1930, 10, 197) examined microscopic sections from 11 cases of benign giant-cell tumor of bone, with a view to determining the histogenesis of the giant cells. These cells were always most numerous where vascular tissue was most abundant. The giant cells formed a portion of the lining of the blood channels, being continuous with the normal endothelial cells lining the adjacent portions. Further, the giant cells were in immediate contact with the blood stream and not separated from it by the interposition of an endothelial lining. From

the examination of serial sections and direct observation of single sections it was concluded that the rounded spaces frequently observed in the cytoplasm of the giant cells were excavations, or hollows, which communicated directly with the lumen of bloodvessels, and represented the lumen of newly formed bloodvessels. The author concluded that the giant cells of benign giant-cell tumors of bone arose from the endothelium of the blood capillaries.

Epidermoid Carcinoma of the Head and Neck with Special Reference to Metastasis.—WILLIS (*J. Path. Bact.*, 1930, 33, 501) has undertaken an analysis of a series of cancerous tumors of the head and neck with respect to the secondary distribution arising from them. The cancers he was dealing with were located upon the lip, tongue, tonsil, palate and pharynx, and occurred in individuals ranging from forty-five to seventy years of age. The average age at the time of death was sixty. Other than the regional lymph glands these tumors are prone to invade (50 per cent) distant organs. The most common localization was in the liver, next in frequency in lung, bone and kidneys. These tumors infiltrated the walls of veins, producing in them an intravascular thrombus permeated by malignant cells. From these intravascular growths distant dissemination may occur. The author believes that the tumor cells do not pass through the pulmonary capillaries, but after inducing a new growth in the lung a new venous dissemination arises from this point.

Gelatinous Degeneration of the Bone Marrow.—MICHAEL (*J. Path. Bact.*, 1930, 33, 533) examined the bone marrow from 480 autopsies, and among this number he found 11 cases of gelatinous degeneration which were quite distinct from edematous processes of these tissues. The most common disease with which this condition was related was tuberculosis, and next came carcinoma. The condition was much more common in males than females, and appeared at about the fortieth year. The condition differs from uncomplicated edema of the bone marrow in the presence of precipitated fibrin about the periphery of the fat cells. The author states that it is apparently the result of a reaction of fat and edema in the presence of fibrinogen.

Phagocytosis by Bronchial Epithelium in the Lungs of Mice.—During the last twenty years the study of pneumonia and other diseases involving the lung has led to a detailed analysis of all the constituent tissues comprising this organ. There is, however, evidence of the phagocytic capacity of certain pulmonary tissues for foreign particles arriving in the pulmonary alveoli. The various investigators have lacked agreement concerning the nature of these phagocytic cells. Some have endowed the alveolar epithelium with this property; others believe that the active cells found in the alveoli have come from the blood stream; others, again, believe that these cells are special histiocytes lying in the vicinity of the various channels within viscera; while still others believe that the phagocytic cells have an origin from vascular epithelium. DUTHIE (*J. Path. Bact.*, 1930, 33, 547) has again investigated the nature of the phagocytic cells of the bronchi and bronchioles and has come to the conclusion that they have an epithelial origin from the lining membrane of these tubes.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

An Outbreak of Food Poisoning Caused by Salmonella Enteritidis.—D'AUNOY (*J. Infect. Dis.*, 1929, 45, 404) reports an outbreak of food poisoning following the ingestion of cream puffs infected with *Salmonella enteritidis*, which affected 90 persons. All patients recovered. Agglutinins for a recovered strain of *S. enteritidis* and for old laboratory cultures were noted in 2 cases, in one of which an acute endocardial involvement developed during the course of illness. None of the food handlers showed agglutinins for this or closely related microorganisms, nor could any significant forms be isolated from their feces. *S. enteritidis* was isolated from rodent excreta found in the bakery, as well as from the intestinal contents of mice trapped therein. Intraperitoneal injection of the recovered organism in mice and guinea pigs caused death, but feeding live and killed cultures to a limited number of rabbits and guinea pigs produced no observable symptoms.

On the Inheritance and Racial Distribution of Agglutinable Properties of Human Blood.—Studies reported by LANDSTEINER and LEVINE (*J. Immunol.*, 1930, 18, 87) substantiate the view that an agglutinable property of human blood detected by an agglutinin present in certain exceptional human sera ("extra agglutinin 1") is inherited and that its frequency shows a racial difference in the two populations examined. Consequently, it must be considered as a constitutional property. The same conclusion seems to hold for other properties of red cells demonstrable by a typical human sera. Evidence is presented to show that the qualities characterizing two subgroups are inherited. The experiments reported were made with the use of some atypical sera containing agglutinins of marked activity.

Milk-borne Septic Sore Throat and Scarlet Fever.—SCAMMAN (*Am. J. Pub. Health*, 1929, 19, 1339) declares that 87 milk-borne outbreaks of scarlet fever have been recorded in the United States from 1893 to 1928, and 45 milk-borne outbreaks of septic sore throat from 1908 to 1928. Fifty-five per cent of all the milk-borne outbreaks of scarlet fever and septic sore throat recorded were in Massachusetts and New York. About three-fourths of the recorded outbreaks of both diseases had their onsets between December and May. In 82 per cent of the outbreaks of scarlet fever a milk handler was the probable source of

infection, as compared to 55 per cent of the outbreaks of septic sore throat. In certain milk-borne outbreaks of both scarlet fever and septic sore throat in Massachusetts there was an unusual proportion of cases aged fifteen years and over. In the Lee outbreak of septic sore throat a cow was found to be infected with a *Streptococcus epidemicus*. In the Charlton outbreak (clinically septic sore throat) the source of infection was the dairyman or his family, all of whom had scarlet fever except the mother, who had a septic finger. No infected cow was found. In the Plymouth outbreak of scarlet fever the probable source of infection was a milk handler. Two cows were found to be infected. The bacteriologic evidence showed conclusively that the Lee outbreak was caused by a streptococcus of the epidemicus type. Studies of organisms from the throats of patients in the Charlton outbreak showed them to be definitely not of the epidemicus strain, but closely related to the scarlatiniform strain. Cultures from the Plymouth outbreak of scarlet fever, on the other hand, were reported of both the epidemicus and scarlatiniform types.

A Survey to Determine the Prevalence of Tuberculous Infection in School Children.—HETHERINGTON, MCPHEDRAN, LANDIS and OPIE (*Am. Rev. of Tuberc.*, 1929, 20, 421) state that tuberculin tests of school children of Philadelphia show that 37.7 per cent are infected with tuberculosis at the age of five years and 90.2 per cent at the age of eighteen years. These figures indicate that there has been no significant diminution of the incidence of tuberculous infection during childhood to correspond with the diminution of mortality from tuberculosis in recent years. The intracutaneous tuberculin test is the only accurate method of determining the incidence of tuberculous infection in apparently healthy children. Accurate information concerning the frequency of infection at different ages in children of different localities, preferably repeated at periodic intervals, would give valuable information concerning the epidemiology of tuberculous infection. American-born children of Italian parentage have shown a low incidence of tuberculous infection as indicated by the tuberculin test. In Jewish children the incidence of the positive reaction has been approximately the same as that of other children. Pulmonary tuberculosis recognized by roentgenologic examination in association with symptoms and physical signs is found in 0.5 per cent of children attending school, being more frequent in high-school children than in children of elementary schools. Sanatorium treatment or its equivalent offers to these children the best chance of recovery from the disease. Latent apical tuberculosis recognizable in roentgenologic films is often the precursor of the adult type of pulmonary tuberculosis. It is found in 1 per cent of adolescent children (of high-school age) and is more frequent in girls than in boys. Children with this lesion should be under continuous observation and should pursue a modified high-school regimen directed to prevent further progress of the lesion. Latent tuberculous infiltration of the lung of childhood type was found in more than 1 per cent of the children. This lesion may be the precursor of grave disease. Children who have it should be kept under observation and should receive special care until it is evident that the lesion is not longer progressive. Latent tuberculous foci in lungs and tracheobronchial lymph nodes are found in more

than 10 per cent of the school children. It may be the precursor of pulmonary tuberculosis. It varies from massive caseous lesions of serious import to firmly calcified foci, which are evidently healed. Its significance is determined by the size of the lesion, the activity of tuberculin reaction, continued exposure to open tuberculosis, associated changes in the lung substance and the age of the child. Pulmonary tuberculosis recognized by roentgenologic examination together with symptoms and physical signs is found more than twice as often in adolescent girls as in boys of the same age. Our figures indicate that it is approximately four times as frequent in colored as in white children of high-school age. The evidence obtained suggests that tuberculous infection may spread within schools but under the existing system of medical school inspection this seldom occurs.

Undulant Fever. Etiology, Epidemiology and Laboratory Diagnosis.—HARDY (*J. Am. Med. Assn.*, 1929, 93, 891) states that the characteristics of *Brucella melitensis* organisms have only recently been fully described. A classification of strains isolated from human beings cannot now be regarded as a reliable index of the importance of the different varieties as a cause of human disease. A special study should be made to obtain a detailed postmortem study in all fatal cases of undulant fever. The pathologic lesions and clinical signs of *Brucella melitensis* infections in animals show a definite correlation. The epidemiologic data, based on the reports of more than a thousand recent cases of undulant fever in the United States, indicate that cattle and hogs with contagious abortion are the source of these infections. Macroscopic agglutination tests on patients with febrile illnesses of undetermined etiology should be made more frequently. Additional study is essential in order to determine effective and applicable methods of control.

Experimental Transmission of Endemic Typhus of the Southeastern Atlantic States by the Body Louse.—The existence of endemic typhus in the southeastern states, apparently not dependent on importation from abroad or from Mexico, has been recognized only within recent years. Its distribution and epidemiology have been carefully investigated by MAXCY (*U. S. Pub. Health Rep.*, 1928, 43, 3079; 1929, 44, 589, 1735), to whom we owe most of our present knowledge concerning typhus as it occurs south of the Potomac. The most important conclusion which Maxcy drew from his epidemiologic inquiries is that endemic typhus is not transmitted by *Pediculus humanus*. MOOSER and DUMMER (*J. Infect. Dis.*, 1930, 46, 170) report experiments which, while showing conclusively that the virus of typhus from North Carolina is able to survive and multiply in the body louse, are not intended to be exploited against the hypothesis of Maxcy. The epidemiologic peculiarities of the disease in that part of the country make it highly probable that the relatively rare cases of typhus originate from a reservoir of virus existing outside of man. Maxcy suspects certain rodents and his demonstration that the white rat is highly susceptible to his virus points in this direction, especially since the gray rat shows the same susceptibility. It is, however, evident from the present experiments that the virus of typhus in the southern states can be transmitted by the human louse once it has gained entrance into man from Maxcy's hypothetical reservoir.

An Anemia of Dogs Produced by Feeding Onions.—SEBRELL (*U. S. Pub. Health Rep.*, 1930, 45, 1175) while testing the effect of various diets in an attempt to evaluate their blacktongue preventive qualities found that onions produced a severe anemia. The condition was a temporary one as the blood returned to normal, even if the onion-containing diet were continued. The white cells were not changed.

Undulant Fever in Ware County, Georgia.—ATWOOD and HASSELTINE (*U. S. Pub. Health Rep.*, 1930, 45, 1343) report 22 cases of undulant fever in Waycross, Georgia, and vicinity in 1928 and 1929; the disease had not been recognized earlier. The cases were clinically characteristic and the diagnosis in most was confirmed by laboratory tests. The time spent in bed varied from four to eleven weeks. The sexes were about equally infected; the youngest case was fourteen years of age, the oldest fifty-six; occupation was not a factor. No case occurred among persons using pasteurized milk and all but one of the 9 intensively studied used raw milk from a single dairy. The cattle supplying milk to the city were found to be infected with the organism of contagious abortion.

Corrections.

1. In the abstract, entitled "The Medical Treatment of Spastic Conditions in the Alimentary Canal" (*AM. J. MED. SCI.*, September, 1930, 180, 433; Department of Therapeutics), the doses of Loehr's formula are incorrectly stated due to misprints in the original article (*München. med. Wchnschr.*, 1929, 76, 1869). In correspondence with the authors he states that the formula should be as follows:

Atropin sulphate,	0.0005
Papaverin,	0.025
Dial,	0.1

2. The photographs, but not the legends of Figs. 1 and 8 of Dr. Lloyd B. Dickey's article, on "The Etiology of Erythema Nodosum in Children," in the October number, have been transposed, so that the photograph at present over the legend "Fig. 1" should be over the legend for Fig. 8 and *vice versa*.

THE EDITORS.

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ORIGINAL ARTICLES.

ROENTGENOLOGY OF THE THYMUS IN INFANCY AND
DIFFERENTIAL DIAGNOSES OF ENLARGED THYMUS
AND ITS TREATMENT.

BY HENRY K. PANCOAST, M.D.,

PROFESSOR OF ROENTGENOLOGY, UNIVERSITY OF PENNSYLVANIA; ROENTGENOLOGIST
TO THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

(From the Department of Roentgenology, University of Pennsylvania.)

ROENTGENOLOGY of the thymic gland in infancy has received very wide attention since Lange¹ in 1911 published the report of his studies from the standpoint of treatment of the condition of enlarged thymus. The subject has been discussed so generally in literature and there exist so many conflicting views in regard to the cause of thymic death and the potential dangers of the structure in question that one hesitates to introduce any ideas that may be empirical. Notwithstanding the wide discussion, there seems to be very little positive or exact knowledge concerning the potential dangers of thymic enlargement, from either the roentgenologic or other view points, that will warrant anyone in dogmatically agreeing with any single theory. Personally, however, we believe that we have ample justification in basing our own conclusions upon phenomena that can be directly observed during life in a large number of individuals presenting clinical evidences of thymic enlargement and upper respiratory tract obstruction. This being the case, we have concluded that the study of the thymus in infancy, where it assumes relatively large proportions, should be approached through observations of the upper respiratory passages.

The vigorous controversy regarding the exact cause of death in cases of supposed status lymphaticus or enlarged thymus has been waged for well nigh a century. The so-called thymic death has been ascribed to a wide variety of causes. Recently these have been conveniently abstracted and summarized by Marine (1928).² The one theory which seems to be most popular at the present time regards the calamity or potential danger as due to the pressure of an enlarged thymus upon the trachea, bloodvessels or nerve trunks. (Kopp,³ Jackson^{4, 5, 6} and Noback.⁸) A second theory ascribes death to a constitutional defect manifesting itself through an injurious raising of the vagus tone, together with a deficiency of the chromaffin system and weakness of the sympathetic system. (Paltauf,⁹ Wiesel¹⁰). Another cause of death that has been stressed is a hypersusceptibility to physical and chemical agents. (Kundrat,¹¹ Blake.¹²) A fourth theory is anaphylaxis. (Symmers.¹³) Finally, a fifth ascribes death to an abnormal thymic secretion of a general lymphotoxemia. (Svehla,¹⁴ Escherich.¹⁵)

Personally, as previously stated elsewhere,^{16, 17} we have followed the trend of most roentgenologists and pediatricists who have seen the wisdom of being on the safe side in the thymic controversy and of recognizing the condition of enlarged thymus as an entity. Our views have been further greatly strengthened by the observations and the statements of Jackson.^{4, 5, 6} We believe, therefore, that the potential danger in the infantile thymus lies in its ability to enlarge further and to compress the trachea and the recurrent laryngeal nerves, and to cause other phenomena due to respiratory obstruction. We have observed all of these occurrences roentgenographically and fluoroscopically in the living infant and we have the statements of Jackson upon observations made directly in the respiratory passages during life. Our beliefs and our remarks do not in any way apply to the cause of supposed thymic deaths in adults. We do not believe that compression is a possible cause of death during adult life.

Jackson,⁴ in 1907, made the following statement: "It has been my privilege, with the aid of the bronchoscope, to demonstrate beyond all doubt on the living patient the purely mechanical nature of thymic asthma in one instance. This, of course, does not prove that every case has this same pathological mechanism, but it does prove the occurrence of that which many . . . have denied, namely, that a hypertrophic thymus can compress the trachea sufficiently to obliterate its lumen . . . it would seem more accurate to call it thymic tracheostenosis." He further suggested: "Let thymic asthma be applied to cases supposed to be associated with neuropathic, convulsive, lymphatic, rachitic, hemic or other pathology, if desired, until their exact pathological mechanism shall have been demonstrated." Jackson,⁵ in 1915, made the following statement, based upon further observations: "Thymic deaths

under anesthesia attributed to 'status lymphaticus' and 'hyperthymization of the blood' are nothing more or less than arrested respiration due to obstructive pressure of the engorged thymus. Artificial respiration is useless, as air cannot be drawn into the lungs, although it can be forced out. After death the engorgement factor is not evident." In a recent personal communication, Jackson⁶ stated that "over 300 cases since that time have been observed bronchoscopically, showing compression and the purely mechanical character of wheezing, dyspnea and the impending asphyxia from thymic pressure." "The upper orifice of the thorax is a rigid ring, and coughing, choking and hard breathing jam the large thymus into this ring and compress the trachea. After asphyxia the thymus shrinks because engorgement is depleted, and at autopsy the thymus is no longer compressing the trachea."

Further substantiation of our belief in the compression theory is to be found in the anatomic studies of Noback.⁸ According to his investigations, the thymic gland is usually cervicothoracic in location and it is wedge-shaped, with the base below and the apex above. (Figs. 7 and 8.) The apex of the wedge passes upward and through the thoracic inlet in 80 per cent of cases. He believes that the broad type of gland described as typical of the newborn soon becomes molded after the establishment of respiration by the expanding lungs into a more elongated mass. A thymus that is not broad may become thick and press on structures behind it. Our roentgenologic studies made during the two phases of respiration have proven that the thymus is pushed upward during expiration, and it is easy to understand how the apex of the wedge jams up into the narrow, rigid, bony thoracic inlet and compresses other yielding structures such as the trachea, vessels and recurrent laryngeal nerves. (Figs. 7 and 8.)

In view of these observations of an eye witness of actual conditions during life, of the postmortem findings of the character of the gland which readily lends itself to causing pressure, and the confirmation of both by roentgenologic studies, we, who have almost an equal opportunity to confirm these findings in the living, and under circumstances intentionally made conducive to engorgement of the gland, cannot do otherwise than take the stand that the danger in the thymus lies in the possibility of its causing pressure stenoses under certain circumstances. Even if it cannot be proven that actual death results from thymic compression, we have sufficient evidence to lead us to believe that obstructive phenomena and cyanosis can result. It may be that another factor is essential in the causation of asphyxia and death. We know from experience that at least one such factor is possible, namely, recurrent laryngeal paralysis, which is a complication of thymic enlargement, to be discussed later.

Every roentgenologic investigation of the respiratory tract in

infancy and early childhood for any purpose should include a collective study of the nasopharynx, oropharynx, the neck and the chest. Thymic cases are obviously referred for examination because of obstructive symptoms, and experience has taught us that obstructions anywhere in the upper passages may produce phenomena simulating those due to thymic enlargement. A differential diagnosis is imperative and must be made when any condition other than thymus may be present. Many times patients have been referred for thymic examinations, and if a thorough search had not been made, obstructive conditions equally as serious, or even more so, would have been overlooked, such as retropharyngeal abscess, foreign bodies or diphtheritic stenosis. Many suspected intrathoracic conditions besides thymic enlargement may be explained entirely or in part by obstructive lesions or phenomena higher up. At a recent examination of a baby, a suspected tracheobronchitis was confirmed, but our wide anatomic inclusion revealed the presence of a button in the nasal passage on one side. This unsuspected foreign body was no doubt indirectly responsible for some of the symptomatology. During infancy, one never knows what condition may be encountered, and as long as we have a technique for wide inclusion applicable to all, it is the one of choice.

In the detection of conditions in the upper portion of the tract, or upper air passages, down to the bifurcation of the trachea, the basis for diagnosis is the fact that these passages consist of a more or less rigid, air-containing tube surrounded by soft tissues, and lying close to the rigid vertebral column. The lumen of the passage throughout can be visibly encroached upon or displaced by extrinsic or intrinsic lesions. The dense vertebral bodies occupy a fixed relative position for the determination of displacements or making comparative measurements of the various portions of the tract and their locations. Moreover, the spine is rigid and will not yield to extrinsic lesions, therefore they must displace or compress the yielding open tube.

Accurate studies of the chest and upper respiratory tract of infants and young children must be based upon two very important problems—a uniform and comprehensive technique capable of exact reproduction in every instance and the establishment of a normal for different ages.

Roentgenographic Technique.—In infancy and early childhood when the thymus and foreign bodies play such an important part in diagnosis and almost any condition must be looked for we have made our technique adaptable for all examinations. It is the one rather generally in use, with certain slight modifications. A preliminary fluoroscopic study is always imperative. It must be made in the horizontal position because of the age period, and in essentially the same horizontal positions as for the roentgenographic views if the latter are to be made with the patients placed horizontally. At any rate, the patients must be fluoroscoped in both the sagittal and lateral directions. The neck must be included with the chest. The

observer's eyes must be well accommodated before beginning fluoroscopy, and in emergency cases one must wait until the proper time arrives for perfect vision. The child should be crying in a regular manner, or at least, deductions must be based upon such crying, and not on sobbing or irregular or jerky respirations. One looks, of course, for any obvious intrathoracic lesions. The movements of the diaphragm domes must be carefully observed and the relations of the mediastinal shadows to these and any abnormalities at the two phases of respiration carefully noted. One should carefully observe the appearances of the pharynx, larynx and trachea and their relations, especially during the two respiratory phases.

Roentgenographic exposures may be made according to either a horizontal or a vertical technique or both. In our horizontal technique the patient is placed upon a rather low table with the tube target raised 38 inches above the cassette. For the sagittal views, the infant is placed prone, with its chest and neck upon the cassette. The tube target should be directly above the level of the suprasternal notch. One attendant holds the hips and lower extremities flat and a second holds the upper extremities *above the head*. The head must be held exactly straight, midway between flexion and extension and without the slightest rotation to either side. One exposure must be made during inspiration and one during expiration, every effort being directed toward getting them at the peak of each phase. The child must be forced to cry because of the greater accuracy in timing the phases and the deeper respiratory effort. It must be crying lustily and regularly because of the greater accuracy of the effects of such respiratory efforts. Sobbing or "catchy" crying not only makes it more difficult to select the exact phases necessary and at their peaks, but typical respiratory changes in appearance will not be shown. The expiratory exposure should not be made at the end of a long breath-holding period. The exposures must, of necessity, be rapid, not over one-twentieth to one-fifteenth of a second, an appropriate milliamperage being used to make this time exposure correct. The patient is next placed on one side or the other. The arms are held *downward and backward* so that the shoulders are thrown posteriorly as far as possible, in order to clear the neck and upper portion of the chest entirely. The head should be held separately and so elevated that the neck will be absolutely straight with the body and exactly midway between flexion and extension. An exact lateral view of both chest and neck are essential. One exposure should be made at complete expiration and another at the peak of inspiration. Important conditions may be overlooked unless these two lateral exposures are made. The exposure time is approximately twice that for the sagittal views.

For our erect technique we have employed a combination chair and cassette holder which is a modification of the encephalogram chair previously described.^{16, 17, 18} An attendant must hold the arms and head of the child. A single attendant is necessary in this technique whereas two or three are required for the horizontal method. The baby sits on a board seat extending across the two arms of the chair. As babies must be held by hand for both methods as well as during fluoroscopy, it is not wise to have any regular members of the staff serve in this capacity. The distance and other exposure factors are the same in the erect as in the horizontal technique.

In the erect sagittal position the arms are held up on either side of the head. The body is held symmetrically so that the sternal ends of the clavicles will appear equidistant from the spine in the roentgenograms and the trachea in the midline. In the lateral views the head must not be allowed to fall to either side and it must be held midway between flexion and extension. The arms are held downward and backward just as in the horizontal technique. One must be careful to keep the child erect and not

permit it to slouch down, for by so doing the large liver in infancy pushes up the domes of the diaphragm and causes buckling of the trachea or increases that which may already be present.

After examining a large number of normal babies and those referred for various pathologic conditions in both the horizontal and erect positions we first concluded that all examinations should, when possible, be made in both positions.^{16, 17} This has been advised by Remer and Belden.¹⁹ We soon learned that better roentgenograms could be made and with greater ease in the erect posture, but as the infant usually spends most of its time on its back or abdomen we continued to make exposures in the horizontal position also, in order to obtain as nearly as possible a true idea of the usual postural anatomic relations. Jackson,⁴ however, states that the dyspnea in thymic tracheostenosis is worse in the sitting position. Notwithstanding this, the natural tendency of most of us is to raise the horizontally placed child into the erect posture if it becomes dyspneic. What we probably do is to relieve the infant by extending the head and straightening the trachea.

Experience in examining a large number of infants by both methods has taught us that the erect-posture technique is perfectly satisfactory alone and has advantages over the horizontal position. Not only can better roentgenograms be made and with greater ease and fewer attendants in the erect posture, but also the lung fields are more extensive because of the lower diaphragm domes, and in the lateral views these structures are shown at their proper levels and not with the one on the down side elevated as is the case when the child is lying on its side.

We believe that it is absolutely essential to examine all thymic suspects during the two phases of respiration. In the sagittal direction there is a great difference in the width of the shadow of the gland, it being as a rule wider during the expiratory phase (Figs. 1 and 2), and sometimes very much wider. If any comparative measurements are to be made we must have roentgenograms of each phase for the purpose. As a matter of fact, however, we pay but little or no attention to the width of the shadow. The sagittal roentgenograms are of value mainly, as far as the thymus is concerned, to determine thickness or density of the shadow, suggestive of lobation, or lateral deviation of the trachea (Fig. 5). The gland does not obstruct because it is wide, but because it is thick or dense, and this seems to be a rather difficult fact for most examiners to comprehend. Jackson⁶ has stated that lateral compression of the trachea occurs in only about 25 per cent of cases, and we must judge this possibility not by the width of the shadow, but by its density, denoting thickness and possible lobulation or the lateral deviation of the trachea (Fig. 5).

In the lateral views, observation of the two phases is necessary in so far as the thymus is concerned, in order to determine compres-

sion or buckling of the trachea at the thoracic inlet, the amount of collapse during expiration and the exact effect produced by the upward push of the wedge-shaped gland into the inlet (Figs. 3, 4 and 7, 8). Moreover, the lateral view of the neck will show different phenomena in the cervical portion of the upper respiratory tract during the two phases.

Another important reason is to be found in the fact that the thymus may not be responsible for obstructive phenomena, and the two phases are quite essential for the detection of other causes of obstruction which may be detected by this complete method of examination. Moreover, the thymus, by itself, is probably not the only cause of obstructive clinical phenomena as a rule. There is usually some additional and associated cause, as collapse of the soft tissues higher up or recurrent paralysis, both of which will be referred to later. In infancy the thymus is a preponderant structure, and when obstructive symptoms are present it usually comes under suspicion at once, unless there is strong presumptive evidence of foreign body, retropharyngeal abscess, diphtheria, whooping cough or a few other conditions, and either it or any of the other possible causes of respiratory obstruction must be proven or excluded by the examination.

Most of us have been under the impression that cyanosis, which is often associated with thymic enlargement, is another evidence of respiratory obstruction. This is not necessarily the case, although we have no way of determining just how often it is or is not. Noback⁸ has called attention to the close anatomic relations between the thymus and important bloodvessels. It is closely applied to the superior vena cava on the right side and to the left innominate vein, and sometimes the superior vena cava may be embedded in the posterior aspect of the gland. In several instances Noback noted evidences of compression of the innominate vessels as they passed through the thoracic inlet. One might consider it possible for cerebral disturbances as well as cyanosis to result from interference with the venous return from the neck. In cases of enlargement of the left lobe, the left pulmonary vessels might be pressed upon and cause a general cyanosis which could be mistaken for the result of a congenital heart condition. We have encountered 2 cases in which both a congenital heart condition and an enlarged thymus were present, and it was only through the greatest care in interpreting our roentgenograms that we were able to determine just when the thymus could be permitted to rest from treatment.

Our ability to diagnose an enlargement of the thymus must be based upon a comprehensive study of the normal. In our determination of normal thymic appearances, we examined 78 presumably normal infants during the first year. All were examined at the ages of two and twelve days, and several at six months. Much of our knowledge of the normal neck or upper respiratory tract was estab-

lished through the collective studies made by Hay.²⁰ To these studies have been added careful fluoroscopic observations of all infants examined for any condition suspected anywhere in the respiratory tract.

A great part of our information in regard to abnormal conditions of the upper respiratory tract depends upon encroachment upon the lumen of or displacement of the pharynx, larynx and trachea. Such deformities or abnormalities of the upper air passages must be estimated by decreased lumen or by changes in the space between their posterior walls and the anterior surfaces of the bodies of the cervical vertebræ. This space and the lumen will vary normally with age, degree of flexion of the neck and the phase of respiration. The phase of respiration has the most marked effect upon the lumen of the pharynx, to be referred to more in detail later. The rigid cartilaginous structure of the larynx prevents changes in its lumen except the ventricles, under normal conditions. The lumen of the trachea changes decidedly. During the expiratory phase and just as inspiration begins, there is a normal collapse of the trachea posteriorly, due to the absence of the cartilaginous ring structure in this aspect. Jackson⁶ states that the tracheal collapse in infants is as easy as that of the bulb of a medicine dropper and that the normal change in lumen just at the beginning of inspiration is about 50 per cent, but involves only the posterior or purely membranous portion. By bronchoscopic observation the lumen is seen to become crescentic instead of rounded with the hollow of the crescent posterior. Air remains in the horns of the crescentic lumen and the apparent collapse, as observed in roentgenograms, is, for this reason, not nearly as much as the actual amount. It will be noted, however, that during the period of collapse the posterior aspect of the intrathoracic portion of the trachea is blurred, and not clean cut as compared to the anterior aspect. This is because there is air in only the horns of the crescent posteriorly.

It is always necessary to determine whether or not the space between the trachea or the pharynx and the vertebral bodies is normal or widened. Hay²⁰ has proposed an admirable method for making comparative measurements of this space by using the sagittal width of the ossified portion of the body of the fifth cervical vertebra as the index of measurement. This vertebral width he arbitrarily designates as "C." With the pharynx at rest the distance between its posterior surface and the osseous portion of the adjacent vertebræ measures at the level of the epiglottic vallecula approximately as follows: First year, never over 1.5 C; first to third year, never over 0.5 C; third to sixth years, never over 0.4 C; sixth to fourteenth years, never over 0.3 C. In adults the *average* measurement is as follows: Males, 0.2 C; females 0.1 C. These measurements of the retropharyngeal space in infants were made with the pharynx at rest and not during crying. They will vary with crying. As our

present technique includes lateral roentgenograms during both phases of respiration, additional measurements are required for the two phases. These we have not yet completed in connection with our normal cases. Measurements have also been established by Hay²⁰ for the retrotracheal space. As this space does not concern us so much in infancy and early childhood as in adult life, with the exception of the effects of foreign bodies, there is no necessity for giving any of the details here.

In the complete study of the upper respiratory tract, and especially for purposes of differential diagnosis, it is important to observe, either by fluoroscope or roentgenogram or by both, many landmarks bounding the air passages in the neck. In the infant and young child the shadows of the following structures should be more or less clearly shown:

1. The pharynx. This air space has been freely discussed and is always easily recognized. It is continuous with the oropharynx and nasopharynx above, and narrows below as it reaches the vestibule of the larynx and pyriform sinuses.

2. The posterior border of the tongue (Fig. 3) curving down to the base of the epiglottis.

3. The uvula and soft palate (Fig. 4).

4. The epiglottis (Fig. 3) is seen in all satisfactory roentgenograms.

5. The arytenoid cartilages (Fig. 3) are also always visible.

6. The superimposed aryepiglottic folds can often be observed.

7. The superimposed pyriform sinuses (Fig. 3).

8. The vestibule of the larynx is readily located by its boundaries. Its base is the upper border of the ventricular folds. Its anterior boundary is from the base of the epiglottis to the ventricular folds. Posteriorly one sees the arytenoids.

9. The ventricular folds are often demonstrable in the infant. They are always seen in the normal adult under proper exposure.

10. The vocal cords often can be seen.

11. The laryngeal ventricles, when seen, easily determine the ventricular bands and the vocal cords.

12. The trachea begins at approximately the lower border of the cricoid cartilage. The latter is likely to superimpose the vocal cords and often cannot be differentiated in infancy.

THE ROENTGENOLOGIC SIGNS OF ENLARGED THYMUS IN INFANCY OR POTENTIAL ENLARGEMENT may be summarized as follows:

1. Lateral deviation of the trachea, established by the sagittal view (Fig. 5).

2. Narrowing of the trachea at the thoracic inlet during inspiration, and determined by the lateral view (Figs. 3, 4 and 7).

3. More than the normal amount of collapse at the thoracic inlet at the expiratory phase (Figs. 3, 4 and 8).

4. Buckling of the trachea at the thoracic inlet at either phase. This must be based upon a rigidly enforced technique, especially in connection with the position of the head. Flexion is likely to produce an appearance simulating buckling.

If the child is not crying regularly, but is sobbing, a marked collapse of the entire trachea may be produced during the expiratory phase just as inspiration is about to begin, whether the thymus is enlarged or not, whereas the true thymic effect is observed only at the thoracic inlet. This likelihood of error from the improper type of crying has been demonstrated by fluoroscopic studies.

The examination for enlarged thymus as it has been carried out ordinarily in the past does not, we believe, show the *exact* evidences of abnormal enlargement.

Complicating Factors in Obstruction. Our observations have led us to believe that the enlargement of the thymus *per se* and the resulting tracheal compression may not be the only cause of obstruction and the attending phenomena, especially in the more severe cases. There are two additional factors to which little attention has been paid, but when we analyze them and their possibilities we can readily realize their importance. The first is the collapse of the soft tissues of the upper respiratory tract—a contributing factor, and recurrent laryngeal paralysis—a result of the hypertrophy of the gland. Atelectasis and drowned lung must be regarded as more or less a result of thymic tracheostenosis and a complicating factor in the clinical phenomena.

Collapse of Soft Tissues. In infancy and early childhood there is an unusual degree of relaxation of the soft tissues of the pharynx, larynx and aryepiglottic folds. In the adult, the retropharyngeal tissues are relatively thin and closely attached to the vertebræ, whereas in the very young these tissues are very loosely attached. This is one of the important factors in the frequency of retropharyngeal abscess from lymphatic extension of infection in infancy. This looseness of soft structures is quite evident in connection with the aryepiglottic folds and the ventricular and vocal bands in the larynx.

If the pharynx of an infant is studied fluoroscopically and by carefully timed roentgenograms it will be found that its appearance differs very greatly during the two phases of respiration. The pharyngeal lumen is much wider and the retropharyngeal space much narrower during the inspiratory phase, whereas the lumen narrows considerably and the retropharyngeal space widens during expiration, especially just before inspiration begins. These phenomena will not be accurately shown unless the infant is crying lustily and regularly (Figs. 3 and 4). They are evidences of the looseness of soft tissues and these expiratory phenomena demonstrate the tendency of collapse in infancy. The degree of collapse gradually diminishes up to about the third year, after which it is negligible and not noticeable. The finding of the two distinct

appearances on roentgenograms often serves as proof of accurate timing of the inspiratory and expiratory exposures.

In the necks of many infants we have noticed that the shadow of the tips of the arytenoid cartilages closely approximate the lower margin of the epiglottis, especially at the very end of expiration, as the inspiratory phase is about to begin (Fig. 3). This is the position assumed normally during the swallowing act, except that the epiglottis drops slightly to meet the arytenoids, which are carried upward by an elevation of the larynx. The appearance in infancy during respiration was at first regarded as an evidence of unusual soft-tissue relaxation and resulting collapse, but as it was later noted in many clinically normal infants (Figs. 3 and 4), we have learned to regard it as abnormal and as an evidence of collapse only when there is an associated lack of air in the laryngeal vestibule. This combination has been noticed quite frequently in some cases of enlarged thymus.

While unusual relaxation of soft tissues does not in itself cause any definite obstruction to breathing, still, it seems possible that under the stress of obstruction elsewhere in the upper respiratory tract, these structures tend to collapse and this undoubtedly becomes an intensifying factor in the obstruction. Jackson⁶ states that the collapse of loose tissues may aid in the obstruction in any case in which the child has to pull hard just at the beginning of inspiration. Further than this, unusual relaxation of soft tissues does no harm. Sometimes it will produce a peculiar respiratory noise which has often been mistaken clinically for an evidence of thymic obstruction in cases in which we have been unable to find any evidences of abnormal enlargement of the gland. According to Jackson, unusual relaxation and collapse are seen most frequently in association with rickets.

Recurrent Laryngeal Paralysis. We have studied 3 cases in which paralysis of the recurrent laryngeal nerves was a complication of enlarged thymus. These are practically the only nerves which are likely to receive serious pressure as they pass through the thoracic inlet. Boyd²¹ has called attention to the possibilities of this complication from the standpoint of anatomic studies. Based upon clinical observations, she has also suggested that the frequent inspiratory stridor, hoarseness or crowing cry may be due to spasm of the vocal cords from irritation of the recurrent laryngeal nerves. Certainly, if a goiter in the neck, where there are no bony confines, can cause recurrent paralysis, it is easy to understand how much more readily the apex of the thymic wedge jamming up into the bony ring of the thoracic inlet can produce paralysis of these nerves. In our cases, confirmed by endoscopy, either the right or left cord has been paralyzed. Therefore, as either nerve may be involved it is quite possible that both can be.

According to Jackson,⁶ bilateral paralysis is rapidly fatal unless

immediate tracheotomy is performed. He has had to operate three times for bilateral involvement, but never for unilateral involvement. He has observed no bilateral cases since the advent of Roentgen therapy. We are inclined to believe that this condition or complication may have been responsible for at least some of the thymic deaths in infancy. Jackson⁶ states that recurrent laryngeal paralysis is more serious in infants than in adults because of the loose structure of the laryngeal and pharyngeal tissues which aid in the obstruction in the very young.

Recurrent laryngeal paralysis usually persists for some time after the gland has been reduced to a safe size by appropriate treatment. A persistence of symptoms is then not due to thymic pressure, but the fact that symptoms persist should act as a warning to consider endoscopy unless they can be explained in a satisfactory manner. Recurrent paralysis is elusive to the roentgenologist because he cannot detect it, although he may sometimes suspect it through failure to demonstrate the ventricles of the larynx or because of suspicious but indefinite signs of high obstruction without adequate explanation. He should always have the possibility of the complication in mind.

Atelectasis and Drowned Lung. Enlargement of the thymus is likely to be present at or soon after birth. It interferes with proper aëration of the lungs. Chilling of the infant may cause further engorgement of the gland and the outpouring of secretion which cannot readily escape. Atelectasis may result from either lack of aëration or retained secretions. It may involve extensive or small areas. If widespread, there is likely to be the classical mediastinal shift to aid in the diagnosis. The so-called drowned lung from retained secretion will closely resemble atelectasis, especially on the expiratory phase, although its nature is likely to be indicated in the inspiratory phase roentgenogram. Both of these conditions will clear up sooner or later after reduction in the size of the thymus.

Differential Diagnosis. Attention has been previously called to the fact that high respiratory obstruction may be due to many other causes than enlarged thymus, and our method of examination must include every other possible cause of obstructive phenomena. We are often too prone to be misled by the relative preponderance of the infantile thymus and to overlook other possibilities. Moreover, the physician who has had the unfortunate experience of observing cases of thymic death may be too hasty in ascribing obstructive phenomena to the thymus when they are due to other causes. Our experience has taught us that this is quite a frequent attitude on the part of many physicians. Many of the conditions that have been misleading are most surprising. Under the circumstances of personal experience we are obliged to list the following conditions as necessary for discussion under differential diagnosis: Foreign

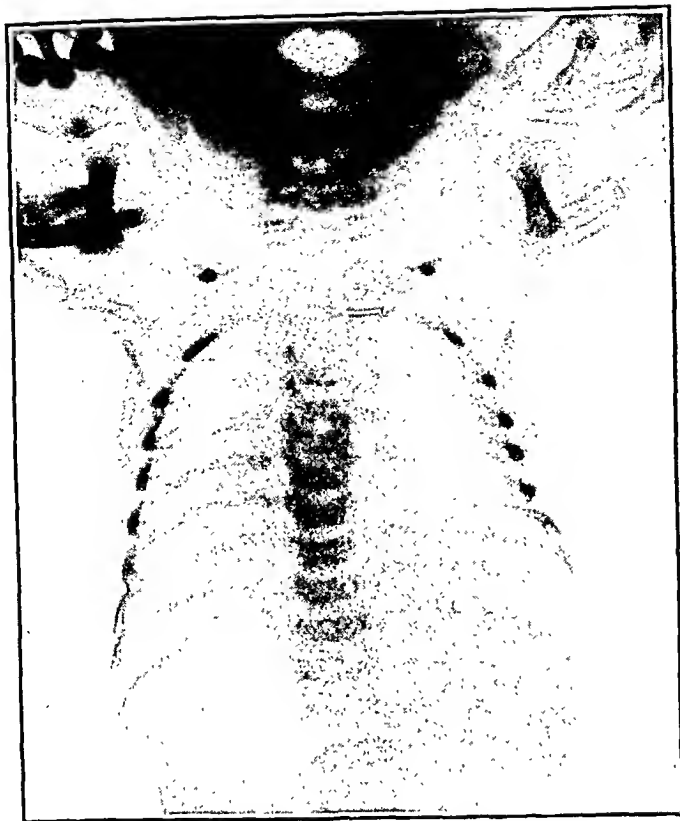


FIG. 1.—Normal thymus. Sagittal view of infant a few days old; expiratory phase, horizontal technique. Note the width of the thymic shadow. This is of no significance in diagnosis. The trachea is not deviated laterally.

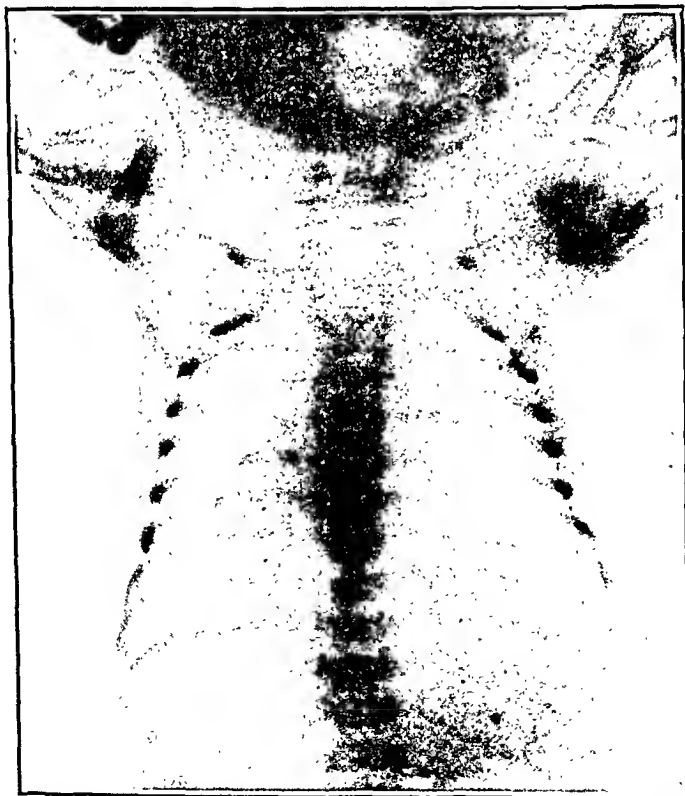


FIG. 2.—Sagittal view of the same case as Fig. 1; inspiratory phase. Note the decreased width of the thymic shadow.



FIG. 3.—Lateral view of the same case as Figs. 1 and 2; expiratory phase. The arrow points to the trachea at the thoracic inlet. There is no buckling and no unusual narrowing of the lumen. A, pharynx (the fact that it is wide open during this phase indicates that the child was not crying properly or that this was not the point of full expiration); B, epiglottis; C, vestibule of the larynx. The vertical shadow behind this is that of the arytenoid cartilages.



FIG. 4.—Lateral view of the same case as Figs. 1, 2 and 3; inspiratory phase. There is no buckling or narrowing of the trachea and, therefore, no thymic enlargement of an obstructive character in this case.

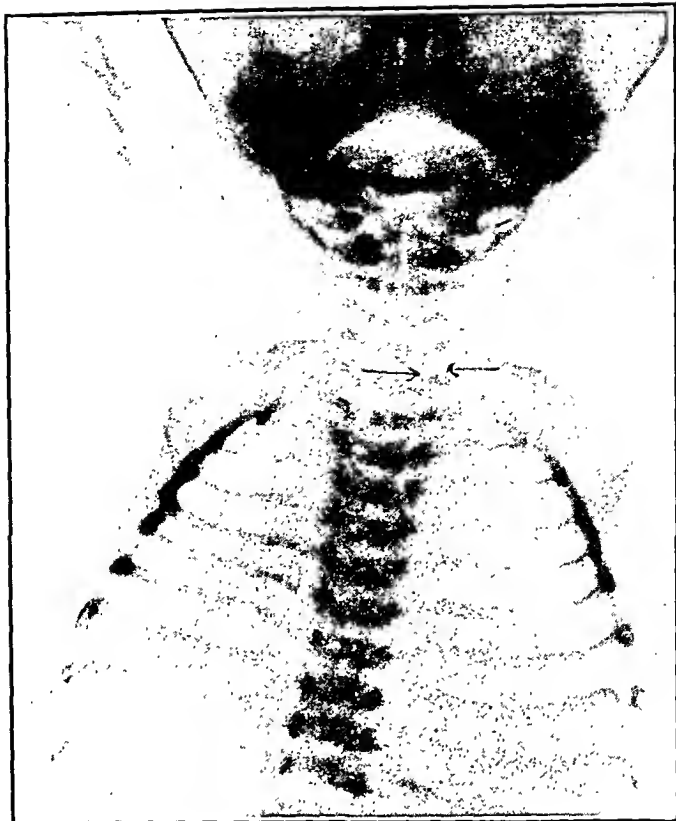


FIG. 5.—Enlarged thymus in an infant, aged three weeks, indicated by a lateral deviation of the trachea during the expiratory phase. During the inspiratory phase it was almost in the midline. The lateral views showed buckling of the trachea at the thoracic inlet and too much narrowing on expiratory phase.

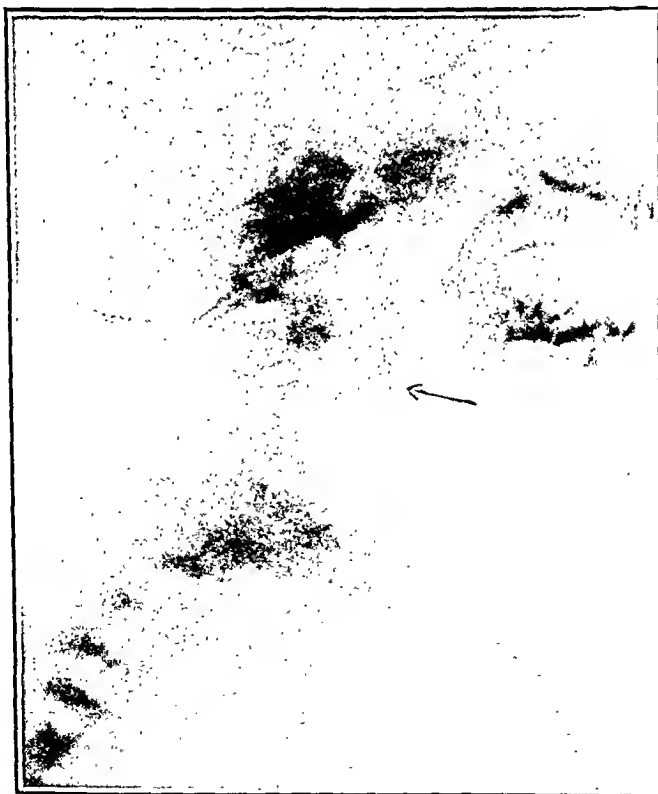


FIG. 6.—Retropharyngeal abscess in a child aged seven months. (Referred by Dr. Tucker.) Note the wide retropharyngeal soft tissue space.

FIGS. 7 to 10.—Roentgenograms of an infant with clinical and roentgenologic evidences of enlarged thymus and upper respiratory tract obstruction and atelectasis of the right lung. Figs. 7 and 8 represent the condition of the chest and upper tract two days after premature delivery at eight months and five hours before treatment. Figs. 9 and 10 show the appearance seventeen hours after treatment.



FIG. 7.—Lateral view, horizontal posture, inspiratory phase. There is marked narrowing of the trachea as it passes through the thoracic inlet behind the apex of the thymus. This should not occur during this phase. The apex of the gland can be seen in this and the next figure.



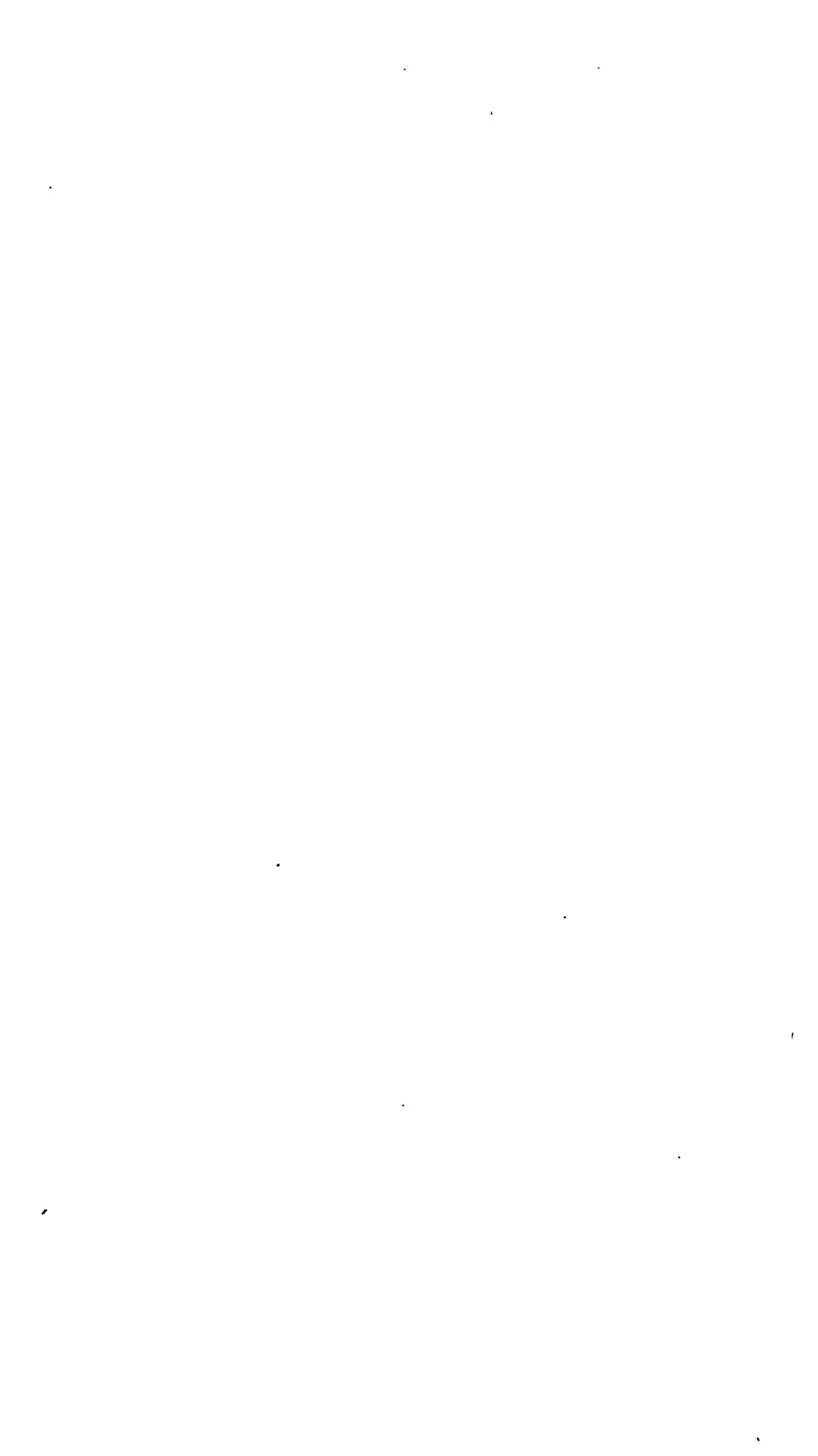
FIG. 8.—Lateral view, expiratory phase. There is a little more than normal amount of tracheal collapse at the thoracic inlet.



FIG. 9.—Lateral view, inspiratory phase. Note how much wider and straighter is the trachea.



FIG. 10.—Lateral view, expiratory phase. This shows about the normal amount of tracheal collapse during this phase.



bodies, retropharyngeal abscess, tracheal and laryngeal stenoses, adenoids, asthma, whooping cough, meningitis, congenital heart conditions, congenital atelectasis, collapse of soft tissues and recurrent laryngeal paralysis. The last three have already been discussed in detail.

Foreign Bodies. One cannot always depend upon a history of foreign-body inspiration in infancy, and especially those belonging to the nonopaque group. Opaque bodies should, of course, be very readily detected even aside from the obstructive phenomena they may produce. The detection of nonopaque bodies depends entirely upon the study of the obstructive respiratory phenomena they induce. Foreign bodies in the trachea produce signs of expiratory obstruction as a rule. Those below the bifurcation cause atelectasis, drowned lung or obstructive emphysema in the distribution of the bronchus affected.

Retropharyngeal Abscess. As retropharyngeal and retrotracheal or retroesophageal abscesses will cause encroachment upon the air passages they may produce phenomena of high respiratory obstruction which have quite frequently, in our experience, been mistaken clinically for those due to enlarged thymus. We have seen cases in which the preponderant thymus of infancy has even thrown the roentgenologist off the track and caused him to overlook an abscess responsible for the symptoms and to regard the thymus as the cause, whereas it was not abnormally large according to our estimations. The diagnosis of abscess is very easy if the technique advised is rigidly carried out and the condition may often be detected roentgenologically before it is suspected clinically. The diagnostic sign is a decided increase in the retropharyngeal or retrotracheal space (Fig. 6). The larger dimension of the retropharyngeal space during the expiratory phase in infancy may be confusing, but the narrowing during inspiration should correct any misapprehension. In the abscess case this narrowing does not occur. In the series of abscess cases reported by Hay²⁰ from our department the retropharyngeal space measured one and a half to ten times the normal for the age of the individual. Unilateral abscess may be difficult to detect, but we were able to make a diagnosis in one such case.

Case Report.—In this connection it is worth while calling attention to a case recently examined by us in which the retropharyngeal space was twice that of the normal for the infant. The case was a cretin, aged four months, referred because of difficulty in breathing and dysphagia and a suspected thymic enlargement. There was no evidence of obstruction from the thymus. Because of the increased retropharyngeal space shown by the lateral view a diagnosis of abscess was made. Endoscopic examination revealed a normal mucosa without swelling but did show that the enormous tongue of the cretin was responsible for the respiratory and swallowing difficulty, partly because of its size and partly because it pushed the larynx downward and backward. A review of our lateral roentgenograms showed that this was the case, and that the downward and backward displacement of the

larynx widened the retropharyngeal space. A contributing factor of more or less importance would be the thickened neck tissues of such a patient. This case is mentioned because of the difficulties in diagnosis which anyone may encounter in connection with an infant cretin.

Retropharyngeal or retrotracheal abscess may occur at any age but varies as to causes and location at different age periods. In infancy and early childhood the most frequent cause is lymphatic extension of infections from all sources which may cause infections of cervical lymph nodes. There is a very free lymphatic communication to the loose retropharyngeal tissues, and lymph nodes are found even in this locality during early life. In the adult, on the other hand, the perforation by lodged sharp foreign bodies such as fish bones, swallowed with food is the common cause, and for this reason, the abscess is usually retrotracheal or retroesophageal rather than retropharyngeal. Even though perforating foreign bodies such as pins, safety pins, jackstones and collar buttons are well recognized causes in children, they are relatively infrequent factors as compared with infections. It is, of course, necessary to exclude a large non-opaque foreign body in the esophagus, such as a piece of potato or bolus of meat, as the cause of a retrotracheal swelling, and also a growth in an adult.

We have been able to diagnose abscess in 26 cases since roentgenology has been used for this purpose. Sixteen of the patients were children and 10 adults. In not a single instance was tuberculous caries of the spine found as a cause, although in 2 adult cases an accompanying osteomyelitis of the vertebræ resulting from gunshot injury was detected.

Stenoses of the Trachea or Larynx. Included in this group of obstructions are streptococcic infection of the larynx, acute diphtheritic infections, postdiphtheritic stenosis, scars as from tracheotomy wounds and congenital stenoses. Streptococcic infections of the larynx may cause considerable obstruction to respiration because of the narrowing of the lumen of this portion of the passage. The lateral view of the neck will show a decided narrowing of the lumen and absence of the ventricles. The arytenoids are likely to be swollen. This appearance can hardly be differentiated from the effect of acute diphtheria.

We have encountered one case of acute laryngeal diphtheritic infection in the larynx. The condition was not diagnosed by us at the time, but the fluoroscopic and roentgenographic appearances denoting high obstruction for which no cause could be found called for an immediate endoscopic examination and Dr. Tucker found the condition in the larynx. At the present time we should be able to detect practically any severe inflammatory process in this structure.

The postdiphtheritic cicatricial stenosis affects particularly the conus elasticus extending from the vocal cords to the first tracheal

ring. The loose tissues in this region, including the cords, are the seat of such intense inflammatory disease as to cause cicatricial contraction afterward, and the cords are usually approximated. In severe cases with perichondritis of the cricoid the larynx is more or less completely obstructed and the upper trachea is also found narrowed considerably or completely stenosed by roentgenologic examination, probably because of the incomplete circumscription by the tracheal rings posteriorly. As pointed out by Hay,²⁰ this is the main point of distinction between the appearances of post-diphtheritic stenosis and the obstruction caused by acutediphtheritic membrane, which obstructs the narrowest portion of the passage in the region of the vocal cords and immediately below. The inflammatory reaction in acute disease will also narrow the entire laryngeal air space. Postdiphtheritic stenoses are very common and should be readily detected, and if found in a thymic suspect, one must be able to decide as to whether or not the thymus is really encroaching on the trachea and just how much of an obstructive factor exists in the stenosis.

There is no reason why traumatic scars and congenital stenoses should not be easily detected by careful technique.

Adenoids. In one instance a thymic suspect was found to have no enlargement of the gland, but the shadow of a large mass of adenoid tissue was found to almost obliterate the nasopharynx.

It may seem strange that such unusual conditions as are discussed in connection with differential diagnosis should be confused with enlarged thymus, but there seems to be a tendency at present to place the blame for any trivial or serious respiratory abnormality in infancy upon this structure. The gland is often unusually wide to physical examination, and although this is not the real menace of the thymus, this very feature may tend to throw suspicion further upon it. Fortunately it is within the power of the roentgenologist to correct these unusual impressions.

Asthma. Asthmatic cases are apt to be confusing to the roentgenologist for the reason that if the examination is made during an attack the phenomena observed during the two phases of respiration simulate those of high obstruction. While he may not find any evidences of thymic compression or distortion of the trachea, he may not be able to explain the phenomena. The best he can do is to make a negative diagnosis of enlarged thymus.

Whooping Cough. The associated tracheobronchitis and spasm of the glottis in this condition may be confusing at times.

Meningitis. In connection with this condition we can cite one case which has been previously reported^{16, 17} and which caused considerable confusion.

Case Report.—A child when seventeen days old was admitted to the hospital as an emergency case because of sudden onset of cyanosis, catchy respiration, occasional twitching of the extremities and, later, general con-

vulsions. It had been sent in as a case of enlarged thymus and this diagnosis was more or less accepted. Careful fluoroscopic and roentgenographic study failed to show any of the signs of thymic enlargement, no evidences of respiratory obstruction and nothing abnormal in connection with the lungs. The child died soon after the examination and a postmortem cisternal puncture proved the presence of a streptococcic meningitis. It is worthwhile considering the possibility of blame upon the treatment had the examination not been made or a negative roentgenologic thymic diagnosis not rendered and the child been treated on the basis of the clinical suspicions.

Congenital Atelectasis. We have become convinced that in some cases of congenital atelectasis the lack of aëration of the lungs may be due to the obstruction offered by an enlarged thymus, and that the nonaërated portions of the lungs may clear up after treatment.

Congenital Heart Conditions. Some of the clinical phenomena arising from congenital heart lesions may be confused with those of enlarged thymus, or both conditions may coëxist. We have had 2 cases in which a congenital heart condition existed, and one of them has many points of interest:

Case Report.—An infant, aged five weeks, was referred for examination for enlarged thymus because of marked cyanosis and some obstruction to breathing. Roentgenograms showed considerable buckling of the posteriorly displaced trachea over the apex of the thymus during the inspiratory phase and there was more than the usual amount of expiratory collapse. A treatment was given on the basis of these findings, although it was not thought likely that the tracheal compression as shown was responsible for all of the cyanosis. Two other possibilities were considered—pressure upon the left pulmonary artery or a congenital heart lesion. The cyanosis was somewhat improved by the treatment but still continued. Another application was made two weeks later and the baby stopped breathing just at the termination and was thought to be dead. Artificial respiration was the only recourse in the emergency and was fortunately successful. Another examination made about two months later showed no tracheal buckling and no unusual collapse. In view of this improvement it was thought probable that the continuance of cyanosis was due to a congenital heart lesion, although this could not be confirmed by roentgenologic study. Eleven days later, a third examination showed a recurrence of the evidences of thymic enlargement and an emergency treatment was given. Over a period of two more months two examinations still showed enlargement and two treatments were administered. The baby died the day following the last treatment.

Autopsy revealed the following conditions: The thymus was very small but the apex *extended well up into the neck* through the thoracic inlet. Evidently the lymphoid structure had been very much reduced by treatment and the continued enlargement was due to the heart condition. When the thymus was removed the thoracic inlet would just admit the index finger, which shows the scant room for all the structures passing through this rigid bony ring. There was a congenital heart lesion consisting of a transposition of the aorta and pulmonary artery and a patulous interventricular septum. The anomaly was not compatible with life.

The baby had considerably more than the usual amount of treatment over a period of five and a half months, although the total application in this time was considerably less than 2 erythema doses. The marked effect

of this upon the lymphoid structure was well shown at autopsy. The apex of the gland was in an unfavorable location and conducive to pressure. The gland, in itself, may not have been too large if the congenital heart condition had not existed, and the latter may have been a decided factor in causing engorgement which would not be affected by treatment. Nevertheless, the reduction in lymphoid tissue by treatment undoubtedly reduced the menace of the engorged gland for a time.

Treatment. We have always felt certain, ever since it was our privilege to discuss the first presentation on the Roentgen treatment of enlarged thymus by Lange¹ in 1911, that the effect of the irradiation was upon the lymphoid tissue of the gland. It was well known to us through our experience in the treatment of leukemia that embryonal types of lymphoid tissue were extremely susceptible to irradiation even with very small doses.

There seems to be some misunderstanding and even skepticism in regard to the rapid effect of irradiation in reducing the size of the thymus. As early as 1905, our irradiation work carried out in conjunction with experimentation by Edsall^{26, 27, 28}, showed that enormous amounts of waste tissue products were very rapidly liberated by irradiation over the spleen in leukemic cases. Aldrich²² states that the results obtained from radiotherapy are often too rapid to be explained by a reduction in the size of the thymus. This supposition, we believe, may be refuted by the following case recently treated and most carefully studied because of the important status of the patient:

Case Report.—The infant was prematurely delivered at eight months. For an hour or two it was exposed to cold and there was afterward an unusual outpouring of respiratory-tract secretion and the infant choked considerably. This was followed by attacks of shallow respirations and cyanosis coming on every two or three hours. It was given oxygen and carbon dioxid inhalations each time and improved and then another attack would occur. These phenomena continued for two days and atelectasis was diagnosed and the question of enlarged thymus arose. At this time the prognosis was considered very grave. A Roentgen examination showed marked narrowing of the trachea at the thoracic inlet and drowned lung on the right side (Figs. 7 and 8). The infant was given a Roentgen ray treatment five hours later. After one hour the oxygen and carbon dioxid were no longer necessary, and a second examination made in seventeen hours showed a normally patulous trachea and a disappearance of the drowned lung (Figs. 9 and 10), and the patient had no further respiratory difficulty.

It has been frequently stated that chilling of an infant followed by the outpouring of secretion is likely to be followed in turn by an associated engorgement of the thymus. This may be true, but irradiation of the gland will not reduce engorgement directly. In another case, treated by us, the engorgement factor may have played a part in the fatal outcome. A newborn and cyanotic infant was brought into our clinic on a cold day and an enlarged thymus was

found by examination. The father was keeping up artificial respiration under instructions from the physician. Treatment was given immediately. The father was requested to leave the baby in the hospital to be watched and given oxygen inhalations. He refused to do this and took the infant home again in the cold and it died, even though artificial respiration was continued by the father. It will be explained later that oxygen and carbon dioxide inhalations are far preferable to artificial respiration, which may be even dangerous. This case, by the way, is the only mortality we have experienced in connection with enlarged thymus treatment with the exception of the two congenital heart cases previously and subsequently mentioned. The latter deaths were not results of the thymic condition, however. We have treated 315 cases of enlarged thymus from 1912 up to April, 1930. Of these 271 have been treated since 1924.

The second congenital heart case just referred to is of interest, first, because of the combination of symptoms arising from the cardiac condition and a slightly enlarged thymus which may or may not have resulted directly therefrom, and, second, for the reason that the autopsy showed the decided effect of slight irradiation upon the gland.

Case Report.—The baby, when two months of age, was referred to us by Dr. Gittings for examination for suspected thymic enlargement because of difficult respiration, slight cyanosis and failure to gain in weight. Roentgen examination showed a dense but not wide thymic shadow in the sagittal views, but there was some lateral deviation of the trachea. The lateral views showed slight posterior buckling of the trachea over the apex of the thymus at the thoracic inlet, but no abnormal narrowing. The cardiac shadow was considerably enlarged to the left. An increased density of the right lung with mottling was interpreted as evidence of drowned lung or retained secretion from partial obstruction of the right main or upper lobe bronchus. There was evidence of considerable soft-tissue collapse into the larynx. The infant immediately received approximately one-sixth of an erythema dose of Roentgen rays over the thymic area. Its condition did not improve and a similar dose was administered two days later, making in all not over one-third of an erythema dose at the skin surface. At this time, because of a systolic murmur and the enlargement of the cardiac shadow, a congenital heart lesion was suspected clinically, and we advised against further treatment. Another examination on the sixth day showed the heart shadow to be larger, the thymic shadow somewhat smaller and normal by lateral views and the lung appearance unchanged. The respiratory difficulties continued. The baby died fifteen days after the first examination and treatment. Autopsy revealed the following conditions:

The thymus was quite small, being approximately 2 by 3.5 cm. in size, and evidently could not at this time cause high obstruction unless possibly under the stress of considerable engorgement. There was a patent ductus arteriosus which produced some stenosis of the aorta at the site of the anastomosis. The aortic arterial blood was shunted into a dilated common pulmonary artery coming off from the right ventricle. From this the right and left pulmonary arteries arose. Dilated right ventricle and auricle compressed the right lower lobe bronchus and possibly the main bronchus.

This was a borderline thymus case and the cardiac condition could have caused the very slight enlargement. The lateral tracheal shift was probably a result of the heart condition. The noticeable decrease in the size of the thymus by roentgenologic study was confirmed by autopsy, and showed the effect of a small dose of irradiation. This death occurred just at the completion of this presentation, and microscopic studies of both cases are just available. In both glands there was a decrease in the cellularity of lymphoid structure. Fibrous tissue was concentrated from diminished size of the glands. The epithelial structure was not changed in any way.

As previously stated, we have been led to assume, by the preponderance of evidence at hand that our treatment is directed toward the reduction of excessive lymphoid tissue in a structure that from its location, anatomic relations and its contour is capable of exerting obstructive pressure upon the upper respiratory tract during infancy. The diminution in the amount of lymphoid tissue by irradiation seems sufficient to reduce the size of the gland to a safe limit whereby it no longer can act as a menace to respiration. It is possible that some of the other theories in regard to thymic death or the potential dangers inherent in the thymus may be true or the conditions they represent act as contributing factors and the treatment may have the same desirable ultimate effect brought about in a different manner. Aldrich²² has recently proposed a very interesting theory in connection with the combination of conditions considered by various authors as status lymphaticus, enlarged thymus and some of the phenomena of vagotonia.

He calls attention to the experimental work leading up to the possible assumption that vagotonia may result from an autonomic imbalance on the basis of suprarenal insufficiency. As the suprarenals of the newborn undergo partial involution during the first two weeks, suprarenal function may be reduced too far in some instances, and if it reaches a sufficiently low point vagotonia may be induced. Suprarenal insufficiency may in addition lessen blood-sugar response to unusual demands and lead to hypertrophy of lymphoid structures, including the thymus.

Aldrich quotes Waldbott²³ as reporting beneficial results in bronchial asthma following irradiation over the spleen. This is, of course, another extensive lymphoid structure. Peterson²⁴ is quoted as stating that irradiation over any large lymphatic structure may result in an effect antagonistic to the vagus, possibly due to a non-specific protein reaction resulting therefrom. If, therefore, relief from vagotonia could result from a nonspecific protein reaction following irradiation of lymphoid tissue, the thymus, being one of the large masses of such tissue would be the preferable structure to treat, and would be preferable to the spleen.

If all of these theories should be true; if suprarenal insufficiency

should be a cause of thymic hypertrophy; if vagotonia should be responsible for certain symptoms believed to be associated with enlarged thymus or adding to their complexity and they can be relieved by the elaboration of nonspecific protein; or if, on the other hand, the symptom complex of obstructive breathing can be laid to a purely mechanical factor inherent in a structure undergoing developmental changes in infancy, the treatment remains the same. Vagotonia and its relief by nonspecific protein elaboration through treatment of a lymphoid structure might be used as an explanation of the results obtained in the relief of pylorospasm and of supposed asthma, especially in older children, by irradiation over the thymic area.

Treatment Technique. In the treatment of enlarged thymus we are dealing with a lymphatic structure which is extremely susceptible to irradiation. There is no necessity to apply a larger dose than is absolutely necessary to reduce the gland to a safe size. As long as we do not know the exact effects of the elaboration of tissue products, it is not wise to give more than just enough treatment to accomplish the desired results. Such a dose could not impair any glandular secreting function of the thymus. The exact dose will depend upon the age and size of the child and the thickness of the chest wall. In very early infancy we employ from one-tenth to one-fourth of a mild skin erythema dose with the following factors: 130 K.V., 5 mm. aluminum filter, $9\frac{1}{2}$ inches target skin distance. Only the entire thymic area is exposed. From the fourth month to the end of the first year, from one-third to one-half an erythema dose is employed, depending on the age and size of the child. Most of the patients are young infants and the dosage is small. No treatment is ever given until after we have had the opportunity of making a thorough study of the neck and chest.

After the first treatment, the baby is to be seen by the physician as often as may seem necessary, and if at the end of a week or ten days, there is any persistence of symptoms, a second application is given. If there is any doubt as to the necessity for this, another examination is made. Further treatment may be necessary, but the average number of applications is two, not including recurrences. Recurrences are to be expected in a fairly large percentage of cases, and require treatment.

During all examinations and treatments care should be observed in not permitting infants to become chilled, for reasons that have already been suggested. Parents should be warned to keep the child warm on the way home.

In preparation of the infant for treatment it is securely wrapped in a sheet, but given ample breathing room. With the baby on its back, the sheet is then fastened with large safety pins between each arm and the body and between each lower extremity to the mattress of the table. A canvas band 6 inches broad, with sand bags at each end, is placed across the knees to keep the legs down. A sand bag is placed against each side of the head and another sand-bag band is placed across these to keep the head down. It does not cover more than the forehead, and a folded towel is placed between the band and the skin. An opaque rubber sheet is placed over the entire body below the thymic area. A fenestrated lead shield is placed over the chest, neck and chin so that only the thymic area will be exposed.

If the infant is breathing badly and there is danger of cessation of respiration in a very serious case that is not struggling, we advise against fixation of the restraining sheet to the mattress in order that measures for resuscitation may be inaugurated quickly should occasion arise. The really serious cases are apt to keep quiet without restraint.

During the treatment of all thymus cases the infant should be carefully watched by a physician member of the staff who will be able to act quickly in case of any untoward obstructive manifestations.

The question naturally arises as to the best procedure to follow in case resuscitation measures are required for suspended respiration. The natural inclination of most of us has been to raise the baby into the erect posture. Jackson⁴ states, however, that thymic tracheostenosis is worse in the erect posture, and yet all of us have seen respiration begin when the child is raised up. What we probably do under the circumstances is to raise the head up and straighten the trachea and thus relieve a certain amount of buckling over the apex of the thymus. One of our first efforts, therefore, should be to straighten the head and trachea. The next natural inclination would be to practice artificial respiration. In this connection, Jackson⁵ further states that artificial respiration is useless in arrested respiration from enlarged thymus because air cannot be drawn into the lungs, although it can be forced out. We have had one experience in which artificial respiration did revive a baby after it stopped breathing (congenital heart case previously referred to). It is possible that engorgement of the thymus may decline to a certain extent after breathing ceases, and artificial respiration may revive the child. Certainly, if it does not do so very quickly, mouth-to-mouth insufflation should be at once adopted as the preferable and safer method of resuscitation.

A very serious thymic case requires very great care after treatment during the period before irradiation takes effect. This is particularly applicable in the newborn, especially when exposed to cold. Such a baby is likely to have atelectasis or drowned lung or both along with the thymic obstruction. It needs oxygen and it requires respiratory stimulation. A mixture of 95 per cent oxygen and 5 per cent carbon dioxid answers the purpose admirably as proposed by Henderson.²⁵ We have observed 2 cases recently in which the inspiration of such a mixture with the tube outlet at the mouth kept the patients breathing safely until the crisis was passed in a very few hours.

Summary. 1. The stand is taken that the thymic menace in infants and young children is largely a matter of tracheal stenosis, aided by relaxation of the soft tissues of the upper respiratory tract. The complication of recurrent laryngeal paralysis is a most serious one.

2. The diagnosis of thymic enlargement has been based in the past largely upon erroneous roentgenologic evidences. The only definite and reliable signs of an enlarged or potentially dangerous gland are abnormal narrowing or buckling of the trachea at the thoracic inlet as it passes over the apex of the gland, and as shown in only the lateral view of the chest, and lateral deviation of the

trachea as shown by the sagittal view. Unusual width of the gland shadow is of no particular significance, and a gland producing a narrow shadow is likely to possess far more inherent danger than a wide one, as shown by the sagittal roentgenogram.

3. The naturally preponderant gland of infancy may be blamed for obstructive phenomena for which it is in no way responsible. The examiner must adopt such a roentgenologic technique as will enable him to detect any other form of upper respiratory tract obstruction which he may be able to show, such as foreign bodies, both opaque and nonopaque, the effect of obstructive specific laryngeal infections upon the lumen of the larynx, postdiphtheritic and other forms of acquired or congenital stenoses, retropharyngeal or retrotracheal abscess, adenoids, atelectasis and unusual collapse of soft tissues. He must have in mind certain conditions that may confuse the diagnosis, and must call attention to them when no discoverable obstruction is apparent, such as asthma, whooping cough, meningitis and congenital heart lesions. The complication of recurrent laryngeal paralysis must be considered when symptoms persist after apparently adequate reduction in the size of the gland.

4. Roentgenologic studies of the respiratory organs of infants and young children should always include the chest, neck and nasopharynx. Sagittal and lateral views must always be made during both phases of respiration, and preferably in the erect posture. The technique is fully discussed.

5. The treatment of thymic enlargement of infancy is discussed in full detail.

BIBLIOGRAPHY.

1. Lange, S.: *X-ray Therapy of Enlarged Thymus*, Am. Quart. Roentgenol., 1911, 3, 1.
2. Marine, D.: *Status Lymphaticus*, Arch. Pathol., 1928, 5, 661.
3. Kopp, J.: *Denkwürdigkeiten in der ärztlichen Praxis*, Frankfurt a. m., 1830, vol. 5 (referred to by Marine).
4. Jackson, C.: *Thymic Tracheostosis*, Tracheoscopy, Thymectomy, Cure, J. Am. Med. Assn., 1907, 48, 1753.
5. Jackson, C.: *Peroral Endoscopy and Laryngeal Surgery*, St. Louis, Laryngoscope Company, 1915.
6. Jackson, C.: *Personal communication*.
7. Jackson, C.: *Bronchoscopy and Esophagoscopy*, Philadelphia, W. B. Saunders Company, 1927.
8. Noback, G. J.: *Contribution to Topographic Anatomy of the Thymus Gland, With Particular Reference to Its Changes at Birth and in the Period of the Newborn*, Am. J. Dis. Child., 1921, 22, 120.
9. Paltauf, A.: *Ueber die Beziehungen der Thymus zum plötzlichen Tod*, Wien. klin. Wchnschr., 1889, 2, 877; 1890, 3, 172. (Referred to by Marine.)
10. Wiesel, J.: *Zur Pathologie des chromaffinen Systemes*, Virchow's Arch. f. path. Anat., 1904, 176, 103. (Referred to by Marine.)
11. Kundrat, R. V.: *Wien. klin. Wchnschr.*, 1895, 8, 1, 26, 44, 64. (Referred to by Marine.)
12. Blake, J. A.: *The Surgical Aspects of Status Lymphaticus*, Ann. Surg., 1902, 35, 745. (Referred to by Marine.)
13. Symmers, D.: *Status Lymphaticus*, Am. J. Dis. Child., 1917, 14, 463. (Referred to by Marine.)

14. Svehla, K.: Ueber die Einwirkung des Thymussaftes auf den Blutkreislauf und über die sogenannte Mors thymica der Kinder, Wien. med. Bl., 1896, pp. 723, 740, 757, 775, 791, 806, 821. (Referred to by Marine.)
15. Escherich, K.: Bemerkungen über den Status Lymphaticus der Kinder, Berl. klin. Wchnschr., 1896, 33, 645. (Referred to by Marine.)
16. Pancoast, H. K., and Pendergrass, E. P.: Roentgenologic Diagnosis of Disease of the Upper Respiratory Tract in Children, Am. J. Roentgenol. and Rad. Therap., 1930, 23, 241.
17. Pancoast, H. K.: Roentgenology of the Upper Respiratory Tract, With Special Reference to Enlarged Thymus and Its Differential Diagnosis; presented before the Interstate Post-Graduate Medical Association of North America, 1929. To be published in Transactions.
18. Pendergrass, E. P.: New Arrangement of Bucky Diaphragm for Encephalography, Am. J. Roent. and Rad. Therap., 1928, 19, 482.
19. Remer, J., and Belden, W. W.: Roentgen Diagnosis and Therapy of the Thymus in Children, Am. J. Roent. and Rad. Therap., 1927, 18, 119.
20. Hay, P. D.: The Neck Roentgenologically Considered, New York, Paul B. Hoeber, Inc., 1929.
21. Boyd, E.: Growth of the Thymus, Am. J. Dis. Child., 1927, 33, 867.
22. Aldrich, C. A.: Symptoms of Vagotonia and Thymic Hypertrophy, J. Am. Med. Assn., 1930, 90, 1119.
23. Waldbott, G. L.: Roentgen Ray Treatment of the Spleen in Asthma and in Related Allergic Disease, Arch. Int. Med., 1928, 41, 683. (Quoted by Aldrich.)
24. Peterson, W. F.: Splanchnoperipheral Balance During Chill and Fever, Arch. Int. Med., 1927, 40, 575. (Quoted by Aldrich.)
25. Henderson, Y.: The Prevention and Treatment of Asphyxia in the Newborn, J. Am. Med. Assn., 1928, 90, 583.
26. Pancoast, H. K.: The X-ray Treatment of Leukemia and Other Diseases of the Blood-making Organs, Trans. Am. Roentgen Ray Soc., 1906, p. 169.
27. Pancoast, H. K.: Experimental and Practical Applications of the X-rays in Diseases of the Blood and Blood-forming Organs, Univ. of Penn. Med. Bull., 1907, 19, 282.
28. Musser, J. H., and Edsall, D. L.: A Study of Metabolism in Leukemia, Under the Influence of the X-ray, etc., Univ. of Penna. Med. Bull., 1905, 18, 174.

REMARKS ON THE PATHOGENESIS OF GRAVES' DISEASE.*

BY DAVID MARINE, M.D.,

DIRECTOR OF LABORATORIES, MONTEFIORE HOSPITAL, NEW YORK CITY.

SINCE Dr. Crile is to discuss the surgical treatment of goiter, while I am listed to say a few words on the etiology of Graves' disease from the standpoint of the laboratory worker, I would like to state my general view regarding the treatment of Graves' disease before going on with the main subject for discussion. I am entirely in agreement with the surgeons that in selected cases the best available treatment, at present, is a well-appointed partial thyroidectomy. I do not believe this is a rational therapy and am convinced that when the etiology of Graves' disease is fully understood, a more rational treatment will be worked out. Twenty years ago it was difficult to get an audience if one stated that the cause of Graves' disease was unknown. Today this is changed. I have long

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been one of those who believe that we must look beyond the thyroid for a solution of so complex a problem. The fact that controversy still involves every phase of the question of Graves' disease proves how complex the problem is.

Classification. The clinical manifestations are so typical and yet so atypical and variable that they have given rise to a great many classifications, even to the point of differentiating separate diseases from what is probably only varieties. This has caused a great deal of confusion. It would be much simpler and more accurate in the present state of our knowledge to divide Graves' disease primarily into *acute* and *chronic* forms, and to divide each of these headings into *complete* and *incomplete* forms. This would eliminate such terms as toxic adenoma, adenomatous goiter with hyperthyroidism, thyrotoxicosis, and a host of other more or less indefinite terms.

Pathologic Anatomy.¹ As regards the pathologic anatomy of Graves' disease, the changes in the thyroid gland have certainly been overemphasized during the past forty years. Opinions as to the significance of thyroid changes have varied from the view that they are constant and specific to the view that they are neither constant nor specific. I hold an intermediate position, namely, that they are constant but not specific. If one allows for the stage of the disease and the age of the patient it cannot be denied that hyperplasia of some degree will eventually occur in all cases if not inhibited by iodine or by some other means. I had the very fortunate opportunity between 1905 and 1915 of studying the thyroids from several hundred cases of Graves' disease in Dr. Crile's Clinic in Cleveland during our studies on endemic goiter. The hyperplasia, however, appears in no way different from the hyperplasia seen in other clinical associations. Thus iodine involutes the hyperplasia of Graves' disease as certainly as it does any other thyroid hyperplasia. The regeneration of the thyroid in Graves' disease is identical with the regeneration of the thyroid following partial removal, and we early came to the conclusion that the thyroid gland is a very labile tissue with a single definite morphologic cycle which can be repeated as often as is necessary in response to stimuli that reduce the iodine store below the critical level. When the iodine store again rises, involution to the colloid state sets in. Much has been made of the occurrence of islands of hyperplastic thyroid tissue in cases of Graves' disease with long-standing goiter. This is due to the fact that, the thyroid being a cystic organ, different groups of follicles stand in different relations to the blood supply, and those with the better blood supply regenerate earlier.

Adenomas of the thyroid as a rule do not react to iodine in this uniform manner but they tend to repeat a similar cycle in a very modified form.

The next most prominent feature of the pathologic anatomy of Graves' disease is the hyperplasia of the lymphoblastic tissues—the thymus, spleen and regional lymph glands. Markham (1856)

first noted the occurrence of thymus hyperplasia in this disease and Marie² (1889) was the first to suggest that the hyperplastic thymus was a regenerated thymus. Thymus hyperplasia is present in 75 per cent of complete cases occurring in individuals under thirty years of age and it is seen less frequently in cases over this age.³ This hyperplasia of the lymphoblastic tissues is reflected in the peripheral blood as a relative lymphocytosis up to 60 per cent of all leukocytes. Theodore Kocher⁴ stressed the diagnostic value of this fact, but today we do not consider it important because other clinical conditions associated with lymphoblastic overgrowth, as for example Addison's disease and status lymphaticus, also have relative lymphotoses. Lymphoid hyperplasia also occurs in the thyroid gland and is tremendously increased in cases that have been subjected to prolonged iodine medication. The significance of the thymus and lymphoid hyperplasia has been variously interpreted. Haberer⁵ and von Mikulicz thought the thymus produced a toxic substance responsible for many of the symptoms and advocated thymectomy as a treatment. In this country the late Professor Halsted also did considerable work on this hypothesis. From the experimental standpoint the lymphoblastic hyperplasia looks more like an antagonistic reaction against an excessive thyroid secretion and a compensatory reaction against some suprarenal-gonadal insufficiency. Thus removal of the thyroid hastens atrophy of the thymus gland, while removal of the suprarenals in animals causes regeneration of the thymus and a clinical and pathologic condition resembling status lymphaticus. This leads to the question of the constitutional state underlying Graves' disease, the so-called Graves' constitution. Some hold that it is always congenital, but I think it also can be acquired. As we have many times pointed out, we believe that Addison's disease, Graves' disease and status lymphaticus are closely related states and that all three are intimately associated with the insufficiency of some secretion of the suprarenal cortex and gonads. In Graves' disease the suprarenals are usually small.

Last, under pathology, I would like to point out the frequency of atrophic changes in the liver. These are of the cirrhotic type and may go on to a well-marked Laennec cirrhosis. It occurs in long-standing cases and I have looked upon it as a manifestation of exhaustion atrophy.

Etiology. In the remaining time I would like to call attention to some clinical and experimental evidence which I think support the view that a deficiency of some internal secretion of the suprarenal cortex and sex glands is one of the fundamental factors in the etiology of Graves' disease, and that the thyroid changes actually represent a compensatory mechanism, although often an injurious one.

1. **SEX AND AGE.** Everyone knows that Graves' disease is from three to six times more common in the female, that is, about the same incidence as in sporadic simple goiter. The reason for this

is not yet clear. As regards age, the disease is comparatively rare before puberty and in the cases occurring after this period I think we can discern two groups: First, those from puberty to the age of thirty years and, second, those occurring during the period of decline in sexual life—in the female roughly between forty-five and fifty-five years and in the male between fifty-five and sixty-five years. The cases occurring early in life I would concede as belonging to the group with the inherited or congenital constitutional anlage which I stated a moment ago is akin to the constitutional defect of status lymphaticus, while the cases developing around the decline of sexual life belong to the group in which the constitutional defect may be acquired. Warthin recently expressed the view that you are born a potential Graves' disease or you cannot get the disease. I do not agree with this view and believe that our studies on the effects of sublethal injury of the suprarenal gland bear this out.

2. EXPERIMENTAL SUPRARENAL CORTEX INJURY.⁷ In the rabbit and cat with intact thyroid a transient symptom complex can be produced by sufficient but sublethal injury to the suprarenals which closely resembles Graves' disease. The outstanding symptoms are increased metabolism, beginning between the third and sixth day and lasting from a week to several months, myasthenia, regeneration of the thymus and hypertrophy of the lymph glands, increased appetite, increased irritability and hypersusceptibility to drugs. This is only a crude reproduction or glimpse of the natural disease. One obvious reason for this crudeness is that the suprarenal gland is at least a dual gland whose functions are to some extent antagonistic, and in injuring the cortex we of necessity cripple the epinephrin-producing medulla. Epinephrin is the most powerful activator of metabolism known, and there is a good deal of evidence that this function is not impaired until late and may even be increased in early Graves' disease.

3. INVOLUTION OF THE SUPRARENAL CORTEX IN INFANTS.⁸ A condition somewhat resembling the experimental suprarenal injuries which I have just referred to occurs normally in newborn infants, namely, the involution of the suprarenal cortex. As you know, the cortex of the newborn infant is unusually large and involution of this hypertrophic cortex begins about the eighth day of extrauterine life, irrespective of whether the infant is a full-term or a premature birth. This involution causes a striking decrease in the volume of the cortex during the next four weeks. We have shown by daily metabolism studies on 10 infants from birth to their thirty-fifth day that coëxistent with this rapid involution of the suprarenal cortex there is a rapid increase in heat production. Thus the heat production in normal infants has been found by various workers (Benedict, Murlin) to average 1.88 calories per kilogram per hour during the first seven days of life. Then between the eighth and fourteenth days it rises about 16 per cent. Our explanation of the hypertrophy of the suprarenal cortex in intrauterine life is that it

has something to do with controlling or inhibiting the rate of tissue oxidation, and after birth this overgrowth involutes in order to increase heat production.

4. SUPRARENAL EMULSIONS IN THE TREATMENT OF GRAVES' DISEASE. A great number of glandular products have been used in the treatment of Graves' disease without much benefit. We have tried in an experimental way most of them, and so far have found only one that has any notable effect, namely, the suprarenal cortex.⁹ Ovarian and corpus luteum emulsions have a similar but less marked effect. In over 50 cases we have found that feeding a glycerol emulsion of very fresh ox suprarenal cortex (glands from which 90 per cent of medulla has been removed) causes a striking gain in body weight and in muscle strength. These effects quite constantly begin to appear after two weeks of feeding. We have not been able to obtain these effects with air-dried preparations, and the value of the emulsion deteriorates rapidly on exposure to air. We look upon this effect as further evidence that the suprarenal cortex and sex glands produce an easily oxidizable substance which plays an important rôle in protecting the individual from Graves' disease, and the loss of which is an important factor in the cause of Graves' disease. Just as in the case of the experimental injuries to the cortex and the spontaneous involution of infants, we think the cortex produces a substance which tends to regulate or control thyroid activity, which is deficient in Graves' disease, whereas the medulla produces a very powerful activator of the thyroid secretion which is not impaired in the developmental stages of the disease.

5. Last, I would like to refer to a case of Graves' disease which more nearly suggests the experimental production of this disease in man than any of the case reports with which I am familiar. The case was called to my attention by Dr. B. S. Oppenheimer. The patient, a physician, aged about forty years, developed what was considered a retroperitoneal sarcoma and was given prolonged deep Roentgen ray therapy. After about two years of this therapy the patient first noted symptoms which later proved to be the early symptoms of Graves' disease, and after six months more of the Roentgen ray therapy he developed complete Graves' disease for which a partial thyroidectomy was performed and was followed by great improvement, though he still has marked exophthalmos and other vestigial signs of the disease. Without any knowledge of the experimental work bearing on the possible relation of the suprarenal cortex and sex glands to the etiology of Graves' disease, this patient had come to the conclusion that there was some connection between the deep Roentgen ray injury of the suprarenals and the onset of Graves' disease.

In conclusion, I would like to point out that while the view that Graves' disease is essentially a thyroid disease still is the prevailing one, and while therapy should still be based on this assumption,

I am convinced that a much more fundamental disturbance lies in a deficiency of some function of the suprarenal cortex and sex glands, which either provides another means of promoting tissue oxidations or has to do with the regulatory control of these oxidations. The most outstanding manifestation of Graves' disease is clearly a loss of control over these oxidation processes, and as a result of this there occurs a physiologic attempt toward compensation by an increased production of the thyroid hormone.

BIBLIOGRAPHY.

1. Marine, D. and Lenhart, C. H.: The Pathologic Anatomy of Exophthalmic Goiter, *Arch. Int. Med.*, 1911, 8, 265.
2. Marie, P.: Sur la reviviscence du thymus dans certaines affections présentant des alterations du corp thyroïde etc., *Bull. et mém. Soc. méd. d. hôp., Paris*, 1893, 3S, 10, 136.
3. Matti: Ueber die Kombination von Morbus Basedowii mit Thymushyperplasie, *Deutsch. Ztschr. f. Chir.*, 1912, 116, 427.
4. Kocher, T.: Untersuchungen des Blut im Basedowii Krankheit, *Arch. f. klin. Chir.*, 1908, 87, 87.
5. Von Haberer, H.: Ueber die klinische Bedeutung der Thymusdrüse, mit spezieller Berücksichtigung des Morbus Basedowii und des Status thymicus, *Med. Klin.*, Berlin, 1914, 10, 1087.
6. Halsted, W. S.: Significance of the Thymus in Exophthalmic Goiter, *Johns Hopkins Hosp. Bull.*, 1914, 25, 223.
7. Marine, David and Baumann, Emil J.: Effect of Suprarenal Insufficiency (by Removal or by Freezing) on the Respiratory Exchange in Rabbits, *Am. J. Physiol.*, 1921, 57, 135.
8. Marine, D., Lowe, Blanche H. and Cipra, Anna: The Possible Influence of Suprarenal Involution in Newborn Infants on Heat Production, *Jour. Metab. Res.*, 1922, 2, 329.
9. Shapiro, S. and Marine, David: Clinical Report of a Case of Graves' Disease with Rapid Improvement Following the Oral Administration of Fresh Ox Suprarenal Cortex, *Endocrinology*, 1921, 5, 699.

THE SIZE OF THE HEART IN GOITER.

A TELEROENTGENOGRAPHIC STUDY.

BY LEWIS M. HURXTHAL, M.D.,

PHYSICIAN, MEDICAL DEPARTMENT, LAHEY CLINIC, BOSTON, MASS.,

AND

O. J. MENARD, M.D.,

ASSISTANT PHYSICIAN, MEDICAL DEPARTMENT, LAHEY CLINIC, BOSTON, MASS.,

AND

M. E. BOGAN, M.D.,

ROENTGENOLOGIST, LAHEY CLINIC, BOSTON, MASS.

(From the Medical Department, Lahey Clinic, Boston, Massachusetts.)

THE question of cardiac enlargement as the result of hyperthyroidism has long been unsettled. One gains an impression from the literature that cardiac enlargement from hypertrophy or dilatation,

or both, is a frequent finding in hyperthyroidism and that it is due in some way to the disease in question. Many statements have been made without adequate statistical evidence to support them. We felt it desirable, therefore, to study by Roentgen ray a consecutive series of 100 patients with hyperthyroidism and compare it with an equal number of patients with nontoxic goiter.

In determining the size of the heart in any individual, the question of slight degree of hypertrophy or dilatation is difficult to settle. Most of the methods in present-day use for determining the size of the heart correlate the area of the frontal silhouette as determined by orthodiagraphic tracing, and the body weight or height, or both. It is obvious that in a group of patients who have lost weight, particularly when the weight loss has been excessive or the patient has been unable to estimate the weight loss, this method of determining heart size is open to question, particularly when slight enlargement is to be decided upon. We have, therefore, simply recorded the heart measurements from teleoroentgenograms in a series of consecutive cases. A few were discarded because of various deformities of the chest or spine. Fortunately, we found that the age distribution was similar in both groups so that justifiable comparisons could be made (Table I).

TABLE I.—AGE DISTRIBUTION BY DECADES IN THE TOXIC AND NONTOXIC GROUPS.

Decade.	Toxic group.	Nontoxic group.
15 to 19	3	1
20 to 29	11	11
30 to 39	22	28
40 to 49	31	30
50 to 59	26	24
60 to 69	7	6
Totals	100	100

The radiographs of the heart in this series were taken at the usual 7-foot distance, with the patient holding his breath neither in full inspiration nor full expiration. This necessarily resulted in some movement and in different degrees of chest expansion, but we felt that the heart shadow would perhaps be quite as near normal and would vary no more than if taken in other ways.

Heart disease may occur in patients with goiter as well as in any other group of individuals. This must be taken into consideration before ascribing cardiac enlargement to goiter. In fact, it has been our clinical impression, based on the examination of many thyroid patients, that in most instances cardiac enlargement in patients with hyperthyroidism is usually associated with some independent cardiovascular disease. In the study of any group of individuals one finds a certain number with cardiac enlargement without obvious clinical or anatomic cause. This group displaying cardiac enlargement would, in most instances, fall in the fourth to sixth decade.

Without known etiology the enlargement would probably be classed clinically as myocarditis or arteriosclerotic heart disease. Plummer¹ reported in 1922 the finding of 63 cases of cardiac enlargement in a series of 617 cases of nontoxic goiter, none of which patients showed hypertension clinically, or other etiologic factors, aside from the presence of goiter. Cabot,² in an analysis of 662 postmortem cases of hypertrophy and dilatation of the heart, found 154 cases without any anatomic cause. Bolinger,³ in Germany, found, on the basis of 1000 postmortem cases, 43 cases of cardiac hypertrophy, also without obvious anatomic cause. (These he ascribed to the excessive amount of beer which was drunk in Munich.) These references are cited merely to show that there are still unexplained causes of cardiac hypertrophy and dilatation. One must, therefore, be careful in ascribing an enlarged heart to goiter when no other anatomic cause can be found.

Diagnosis of Coincident Heart Disease. The diagnosis of coincident heart disease in the presence of hyperthyroidism is frequently difficult. For this study we have classified coincident cardiovascular disease under three headings: that is, rheumatic, hypertensive and miscellaneous. (a) Under "rheumatic" were included those cases which showed unquestionable evidence of valvular disease such as mitral stenosis and aortic regurgitation, with or without a history of rheumatic fever or chorea. Others with less marked evidence, that is, mitral regurgitation, who had a history of rheumatic fever, were classified as rheumatic heart disease. Most of these have been seen since operation and the character of the murmur has not changed. (b) Hypertension was diagnosed, with the exception of 5 cases, in patients over forty years of age who showed a basal systolic blood pressure of not less than 150 mm. Hg. Other evidence was used, such as changes in the retinal or peripheral vessels. A number of these patients showed a basal diastolic pressure over 100 mm. Hg. before operation, and most of them showed it after operation. We know that this criterion does not include all hypertensive cases, but, on the other hand, of 26 toxic cases so diagnosed 25 showed distinct and well-marked hypertension three months or more after operation. Furthermore, we know from follow-up study of the blood pressure after operation for toxic goiter that the incidence of hypertension in this series is that which is to be expected according to each age group.⁴ (c) Under the miscellaneous group were placed those patients who showed evidence of coronary disease and angina pectoris; there was one case of pericardial effusion, one case of acute glomerular nephritis with generalized edema and enlarged cardiac shadow. A diagnosis of arteriosclerotic heart disease was not made in this study because we felt that cardiac enlargement might thus be too easily accounted for and, therefore, subject to criticism. While we know that it existed, we have avoided using it. There were no cases of luetic aortitis found in this series.

The statistical data of the two groups is shown in Tables II and III. It should be mentioned here that the incidence of toxic adenomatous goiter in this series of 100 was higher than we usually find. Furthermore, we found rheumatic fever and rheumatic heart disease present in this group more frequently than we usually encounter it. This was probably largely a matter of chance but, insofar as this study is concerned, it should favor the finding of larger heart measurements in toxic goiter.

TABLE II.—MISCELLANEOUS DATA.

Item.	Toxic goiter.	Nontoxic goiter.
Average first basal metabolic rate	+48.04	+4.5
Average first basal pulse	103	80.9
Average first basal weight in pounds	124	139
Average weight loss in pounds	23.2	0
Average first basal blood pressure	145/70	136/73
Average first clinical blood pressure	163/79	144/86

TYPE II A.—MISCELLANEOUS DATA.

	Toxic goiter.	Nontoxic goiter.
I. Sex:		
a. Males	16	6
b. Females	84	94
II. Type goiter:		
a. Exophthalmic goiter	61	0
b. Recurrent exophthalmic goiter	6	0
c. Adenoma	11	44
d. Multiple adenoma	22	52
e. Malignant adenoma	0	4
III. Arteriosclerosis:		
a. Calcified aortic plaques	8	7
IV. "Rheumatic infection:"*		
a. Growing pains	6	10
b. Tonsillitis	37	34
c. Quinsy sore throat	6	2
d. Chorea	1	0
e. "Rheumatic fever"	19	6

* Rechecked by letters to patients.

INCIDENCE OF CARDIAC ENLARGEMENT. We have arbitrarily chosen cardiac enlargement to mean a transverse diameter of the heart which was 0.9 cm. or more over one-half the inside diameter of the chest. It is obvious that this did not include some cases of cardiac enlargement, but on the other hand cases are also present in this group which are not actually enlarged, particularly in the transverse type of heart. Of the total number, 46 per cent of toxic cases showed cardiac enlargement according to the above standards, while 41 per cent in the nontoxic group were enlarged. Certainly, this is not a striking difference.

RELATIONSHIP TO AGE. In Table III the percentage of heart enlargement is shown according to age group. It is to be noted that where the percentage in the different groups is based upon enough cases to be significant, the number of enlarged hearts appears

to increase with age. These figures parallel closely those published by Coller on "The Heart in Endemic Goiter."⁵

TABLE III.—CARDIAC ENLARGEMENT (0.9 CM. OR MORE OVER CARDIOTHORACIC RATIO OF 1 TO 2) ACCORDING TO AGE GROUPS.

Age groups.	Toxic goiter.			Nontoxic goiter.		
	Total cases.	No. of cases C.T. ratio over 0.9 cm.	Per cent C.T. ratio over 0.9 cm.	Total cases.	No. of cases C.T. ratio over 0.9 cm.	Per cent C.T. ratio over 0.9 cm.
10 to 19 . .	3	1	33	1	0	0
20 to 29 . .	11	3	27	11	2	18
30 to 39 . .	22	9	45	28	9	32
40 to 49 . .	31	15	45	30	13	43
50 to 59 . .	26	14	53	24	13	54
60 to 69 . .	7	4	57	6	4	66
Totals .	100	46	46	100	41	41

RELATIONSHIP OF CARDIAC ENLARGEMENT TO THE DURATION OF HYPERTHYROIDISM. Table IV shows the measurements of the heart as compared with the duration of thyroid toxicity. There seems to be no definite relationship. We feel, however, that this is not absolutely conclusive, since the number of cases of long duration is not sufficient to give reliable averages.

TABLE IV.—CARDIAC ENLARGEMENT (0.9 CM. OR MORE OVER CARDIOTHORACIC RATIO OF 1.2) GROUPED ACCORDING TO ESTIMATED DURATION OF DISEASE—TOXIC GOITER (DURATION UNDETERMINED IN 11).

Duration, months.	No. of cases.	No. of cases C.T. ratio over 0.9 cm.	Per cent C.T. ratio over 0.9 cm.
1 to 11	45	19	42
12 to 23	22	12	54
24 to 35	12	5	41
36 to 47	3	0	0
48 to 59	7	3	42
	89	39	43.8

TABLE V.—CARDIAC ENLARGEMENT (0.9 CM. OR MORE OVER CARDIOTHORACIC RATIO OF 1 TO 2) GROUPED ACCORDING TO ESTIMATED WEIGHT LOSS (89 CASES).

Toxic Goiter.		No. of cases C.T. ratio over 0.9 cm.	Per cent C.T. ratio over 0.9 cm.
Pounds lost.	Total cases.		
0 to 9	13	3	23
10 to 19	32	17	53
20 to 29	21	11	52
30 to 39	9	4	44
40 to 49	11	5	45
50 to 59	2	1	50
60 to 69	1	1	100
Totals	89	42	48

RELATIONSHIP OF CARDIAC ENLARGEMENT TO WEIGHT LOSS. An attempt at correlation between the size of the heart and weight loss is shown in Table V. Again no definite relationship is forthcoming.

We realized here, too, that to come to a definite conclusion in regard to weight loss, which in many instances is a sign of the severity of the disease, we should exclude all cases of known heart disease and compare a large number of such cases who show extreme amounts of weight loss with a group that has lost very little.

A COMPARISON OF THE DEGREE OF CARDIAC ENLARGEMENT IN THE TWO GROUPS. The cases were divided into five groups as follows: The first group consisted of those in which the transverse diameter of the heart was less than, or equal to, one-half the transverse diameter of the chest; the second group included those in which the transverse diameter of the heart exceeded one-half the transverse diameter of the chest by 0.1 to 0.9 cm.; while the other three groups included those in which the transverse diameter of the heart exceeded the transverse diameter of the chest by 1 to 1.9 cm., 2 to 2.9 cm. and 3 cm. or more, respectively (Table VI). The parallelism in the two groups of goiter is striking.

TABLE VI.—VARIOUS CARDIOTHORACIC RATIOS IN TOXIC AND NONTOXIC GOITER.

	Toxic goiter.	Nontoxic goiter.
Transverse diameter of heart equal or less than one-half transverse diameter of chest	27	29
Transverse diameter of heart 0.1 to 0.9 cm. (inclusive) greater than one-half transverse diameter of chest	27	30
Transverse diameter of heart 1 to 1.9 cm. (inclusive) greater than one-half transverse diameter of chest	24	15
Transverse diameter of heart 2 to 2.9 cm. (inclusive) greater than one-half transverse diameter of chest	11	16
Transverse diameter of heart 3 cm. or over greater than one-half transverse diameter of chest	11	10
Total cases	100	100

THE CORRELATION BETWEEN AGE GROUP, CARDIOTHORACIC RATIO, TYPE OF GOITER AND HEART DIAGNOSIS. This distribution for the toxic cases is shown in Table VII. It is to be noted that a greater percentage of hearts apparently enlarged fall in the toxic adenomatous group (66 per cent of toxic adenomatous group enlarged, compared with 35 per cent for exophthalmic goiter), but it also can be seen that those with toxic adenomatous goiter fall mainly in the fourth, fifth and sixth decades. This can account for the greater frequency of cardiac enlargement, due to the greater incidence of cardiovascular disease. Table VIII shows the same correlation for nontoxic cases, except that the discrete adenomas of the thyroid were separated from the multiple adenomatous type. Fifty per cent of the patients with multiple adenomatous goiter showed an increase over the so-called normal cardiothoracic ratio of 1 to 2 by 0.9 cm., whereas only 36 per cent of the cases with single adenoma showed this change. A greater incidence of hypertension in the multiple adenomatous group probably explains this

difference. It might be well to say here that a good many patients are sent to us with hypertension and goiter with the prevalent idea that the two are associated. Thus, a patient who has had a goiter for years might not be taken seriously by his physician, but as soon as a high blood pressure is found operation is then considered.

TYPE VII.—TOXIC GOITER. DISTRIBUTION BY AGE, TYPE OF GOITER, HEART DIAGNOSIS AND HEART MEASUREMENTS. TRANSVERSE DIAMETER OF HEART IN CENTIMETERS OVER CARDIOTHORACIC RATIO OF 1 TO 2.

Age group.	Exophthalmic goiter.				Toxic adenomatous goiter.			
	To 0.9 cm.	1 to 1.9 cm.	2 to 2.9 cm.	3 cm. +.	To 0.9 cm.	1 to 1.9 cm.	2 to 2.9 cm.	3 cm. +.
10 to 19	2 N	1 R						
20 to 29	7 N	2 N						
	1 R	1 H						
30 to 39	9 N	2 N	1 M	..	1 N	1 R		
	1 H	2 R	2 R	..	2 H			
		1 H + R						
40 to 49	9 N	1 N	2 H	1 R	1 R	1 N	1 R	1 H + R
	1 M	3 H	3 H	..	1 H
	3 R	1 H + R						
	2 H							
50 to 59	3 N	1 N	1 R	..	3 N	..	2 H + R	2 H + R
	1 M	2 H	3 H	..	1 M	2 H
	1 R	1 M	1 H + R	..	1 H	1 R
60 to 69	1 N	1 N	1 H + R	..	1 H
	1 H	1 R
								1 H + R

N = Negative findings. H = Hypertension. R = Rheumatic or probable rheumatic valvular disease. M = Miscellaneous.

TABLE VIII.—NONTOKIC GOITER. DISTRIBUTION BY AGE, TYPE OF GOITER, HEART DIAGNOSIS AND MEASUREMENTS. TRANSVERSE DIAMETER OF HEART IN CENTIMETERS OVER CARDIOTHORACIC RATIO OF 1 TO 2.

Age group.	Single adenoma.				Multiple adenoma.			
	To 0.9 cm.	1 to 1.9 cm.	2 to 2.9 cm.	3 cm. +.	To 0.9 cm.	1 to 1.9 cm.	2 to 2.9 cm.	3 cm. +.
10 to 19	1 N			
20 to 29	3 N	4 N	2 N		
	1 H	1 H			
30 to 39	11 N	1 N	2 N	1 H	7 N	1 R	1 R	
	1 R	1 R	1 R	1 M				
40 to 49	9 N	1 R	1 H	..	6 N	2 N	2 N	1 N
					2 R	2 H	3 H	1 H
50 to 59	5 N	2 H	1 N	..	2 N	1 N	1 H	2 H + M
	2 H	..	1 H	..	1 H	2 H	..	1 N
	1 H + R	2 H
60 to 69	1 N	..	1 R	..	1 H	..	1 H	
							1 H + R	

N = Negative clinical findings. H = Hypertension. R = Rheumatic or probable rheumatic valvular disease. M = Miscellaneous.

CORRELATION BETWEEN WEIGHT AND HEART SIZE. We have further distributed these cases according to cardiothoracic ratio, correlating the average weight for each group, the transverse diameter of the chest and the transverse diameter of the heart. This is shown in Table IX. This was done to exclude a possible error in using the cardiothoracic ratio as an index to heart size rather than the area of the frontal plane correlated with body weight. The average weight for the different groups, both toxic and nontoxic types, varies but little. If the average weight loss was 23.2 pounds and was added to each group of toxic goiter, the average weight of both groups would be practically the same, at least so far as it might influence the size of the heart. The transverse diameter of the chest, however, is greater in those groups where the cardiothoracic ratio is normal or below. This might indicate that a number of these hearts were enlarged, but the parallelism of the average transverse diameters of the heart in the two groups would seem to offset this impression.

TABLE IX.—DISTRIBUTION ACCORDING TO VARIOUS CARDIOTHORACIC RATIOS WITH AVERAGE TRANSVERSE DIAMETER OF HEART AND CHEST AND AVERAGE WEIGHT.

Variation from the "normal" C.T. ratio (1 to 2) in centimeters.	Nontoxic goiters.			Toxic goiters.		
	T.D. chest (cm.).	T.D. heart (cm.).	Average weight in pounds.	T.D. chest (cm.).	T.D. heart (cm.).	Average weight in pounds.
— to 0	25.6	11.8	148.0	24.3	11.3	120.0
+0.1 to 0.9	23.6	11.8	141.0	23.8	12.3	120.0
+1.0 to 1.9	24.2	13.1	146.7	23.9	13.4	122.3
+2.0 to 2.9	23.2	13.9	152.0	22.2	13.9	125.2
+3.0	23.9	16.2	151.0	22.5	14.9	120.8

TABLE X.—COMPOSITE HEART AND CHEST MEASUREMENTS.

	Toxic goiter (100 cases), cm.	Nontoxic goiter (100 cases), cm.
Transverse diameter chest (average)	24.1	23.95
Transverse diameter heart	13.01	12.52
Left border	9.04	8.63
Right border	3.96	3.89
Long diameter	13.67	13.28

Discussion. If hyperthyroidism produces any great enlargement of the heart one might reasonably expect to find greater average measurements in a group, such as we have studied. In Table X is given the composite picture of the heart measurements in both groups. These measurements represent simple averages. With the average transverse diameter of the chest the same in both groups, and with the average weight of the nontoxic group within 2 pounds of the estimated average weight in the toxic group based on average weight loss, we believe it is possible to make comparisons

in regard to the actual heart measurements. Accordingly, we find that the average transverse diameter of the heart in the toxic group exceeds the average transverse diameter of the nontoxic group by only 0.49 cm. There is no question that cardiac enlargement, as a result of thyroid toxicity, must be made on a large group and not on individual cases. One must, therefore, conclude that if hyperthyroidism causes cardiac enlargement, that is, hypertrophy or dilatation or both, it does so only to a slight degree. One can hardly conceive of the heart not increasing in weight at least slightly as the result of the excess activity, yet it is remarkable that even in long-standing hyperthyroidism of high degree in younger people the heart is often found to be of normal size. Recent experimental work⁴ has shown some hypertrophy of the heart involved after relatively large doses of thyroid extract in dogs. One cannot reproduce a similar experiment in the human being, but, could it take place, a greater degree of cardiac enlargement than found in this series would be expected.

It might reasonably be asked, is the cardiac enlargement in the nontoxic group herein reported due to the so-called goiter heart from tracheal stenosis? Meyer and Sulger⁷ state that the largest hearts are found in cases with tracheal stenosis. In 125 cases of toxic and nontoxic goiter they found the heart enlarged in 66 cases. Fourteen of these cases, however, showed no thyroid toxicity and no tracheal pressure. Of these 14, 1 was rheumatic, 1 arteriosclerotic and a third had "myocarditis." No reference was made in their study of the age of the patients or blood-pressure determinations. In our toxic cases the largest hearts were associated with tracheal narrowing in only 3 cases and none of these were compressed enough to cause stridor on exertion or at rest. Nor was stridor present in any of the series of nontoxic goiter, but various degrees of tracheal pressure were present. Of those patients in the nontoxic group showing cardiac enlargement without obvious clinical cause, only one showed tracheal narrowing. In a community such as New England where endemic goiter is not prevalent, few cases of severe tracheal stenosis are seen. Thus, our findings may not parallel those found in a goiter belt. The same might be said also of the incidence of rheumatic fever, or rheumatic heart disease associated with goiter in different localities.

In order to exclude the possibility of a low-grade toxemia of some kind affecting the heart, which has often been suggested⁶ in nontoxic goiter, we have undertaken a study of 100 Roentgen rays of nongoitrous individuals of the same age distribution as found in this series.

Conclusions. 1. Teleroentgenograms were made on 100 consecutive cases of toxic and 100 consecutive cases of nontoxic goiter in the Lahey Clinic.

2. No definite relationship could be found between the duration of the disease or weight loss and the size of the heart.

3. Cardiac enlargement as determined by teleoroentgenography showed a fairly direct relationship to age and coincident cardiovascular disease.

4. The number of enlarged hearts of different degrees was practically the same in both toxic and nontoxic goiter.

5. If hyperthyroidism causes cardiac enlargement or hypertrophy and dilatation, it is slight.

REFERENCES.

1. Plummer, H. S.: Blood Pressure and Thyrotoxicosis, *Trans. Assn. Am. Phys.*, 1915, **30**, 450.
2. Cabot, R. C.: *Facts on the Heart*, W. B. Saunders Company, Philadelphia, 1926, p. 424.
3. Bolinger, Prof.: Über die Häufigkeit von Ursachen der idiopathischen Herzhypertrophie in München, *Deutsch. med. Wehnschr.*, 1884, **10**, 180.
4. Hurxthal, L. M.: The Blood Pressure Before and After Operation in Hyperthyroidism (in press).
5. Collier, F. A.: The Morbidity of Endemic Goiter, *J. Am. Med. Assn.*, 1924, **82**, 745.
6. Simmons, J. P., and Brandeis, W. W.: The Size of the Heart in Experimental Hyperthyroidism, *Arch. Int. Med.*, 1930, **45**, 503.
7. Meyer, A. W., and Sulger, E.: Das Kropfherz vor und nach Operation, *Med. Klin.*, 1926, **1**, 838.

EDEMA.

BY HERMAN ELWYN, M.D.,

ASSISTANT VISITING PHYSICIAN, GOUVERNEUR HOSPITAL, NEW YORK CITY.

THE factors responsible for the presence of edema have always been sought for in some change in the local physicochemical factors on one or the other side of the capillary wall or in a change of permeability in the capillary wall itself. There are many reasons why such changes in the local physicochemical factors or in the permeability of the capillary walls are not sufficient to explain the formation of edema. Lately the tendency has been to look for the causes of edema in a disturbance of the water regulation as a whole. Local physicochemical changes alone are never adequate to explain a disturbance in a vegetative function. Although at the bottom of every physiologic process in the organism there is a physicochemical change yet the totality of the process is different from that which takes place in an artificial physicochemical system. The difference is that between physiology on one hand and chemistry and physics on the other. Physiology implies regulation of the physicochemical changes and such a regulation has been developed for each physiologic process phylogenetically for a purpose. The purpose is that of maintaining the physiologic process constant or near-constant under varying conditions. Haldane¹ years ago in a Harvey lecture spoke of the physiology of the normal, meaning thereby that we

have to determine how the organism maintains the various normals. This has been most clearly expressed by Claude Bernard.² He saw that in the more highly developed organism a free and independent life can only be maintained if the organism is able to maintain a constant and uniform internal milieu in contrast to the ever-changing external milieu. As the individual factors of the internal milieu which must be kept at a constant value, Claude Bernard mentions water, oxygen, heat and the chemical and food reserves. The maintenance of constant values is of such importance to the physiologic organism that we can express as a fundamental principle in physiology:

I. The organism attempts to maintain constant values within the normal limits of variation for those substances which it needs in its economy and for those processes to which it has become adapted phylogenetically.

Such constant values are familiar to us in the number of red blood corpuscles in the blood, in the amount of hemoglobin, of sugar, of fat, of salts, and of protein in the blood, in the maintenance of the body temperature, of the degree of oxidation, and of many other vegetative functions. Such constant values are maintained by effector organs which are under the control of the central nervous system, as already indicated by Claude Bernard.

II. It is obvious to ordinary observation that the water content of the highly developed organism is maintained at a constant value. The weight of the individual under uniform external conditions and uniform food intake is practically constant from day to day and is quite independent of the amount of water taken in. An excess of water taken in is promptly eliminated. Water in the organism is contained in the blood stream, in the lymph stream, and in the organs and tissues. The water content of the blood is always found to be constant within the normal limits of variation. And this is as it should be, for were the blood volume to change continually, the maintenance of a constant internal milieu, or for that matter, of the whole circulation, would not be possible. As a matter of fact, the water content of the blood is hardly ever disturbed over a prolonged period, even under pathologic conditions.

The amount of lymph is extremely variable, and dependent entirely upon the activity of the organ from which it comes. When the organ is active the amount of lymph is increased. It evidently forms a buffer between the active organ and the blood stream, and takes up the excess of waste substances and of water.

In the organs and tissues, water is contained as bound water, forming part of the colloidal system of the protoplasm and as free water, which is found between the individual parts of the protoplasm and between cells and tissues. The free water is a variable quantity and varies from hour to hour with the intake of water and with its elimination.

In the colloidal system of protoplasm, the solid phase consists of particles of protein, nucleoprotein and lipoids in combination with electrolytes, and the liquid phase consists of a solution of protein and electrolytes. This system presents an enormous intersurface on which the fundamental biologic processes of oxidation and respiration take place. The stability of such a system is maintained by the difference in potential of the two phases. The electrolytes concerned are hydrogen, hydroxyl, chlorid, phosphate, sulphate, sodium, potassium, calcium, magnesium. A change in the electrolytic distribution produces a change in the phases of the colloidal system, and water is either taken up by the system or given off. The system is in equilibrium with the free water between the individual parts of the protoplasm and between the cells. Water taken up by the system comes from the free water, and water given off goes to increase the free water. Any change in the system must always be preceded by a change in the electrolytic distribution in the phases of the system.

Thus, the water contained in the body is maintained at a constant value in the blood; varies in the colloidal system of the protoplasm with the changes in the fundamental biologic processes of the protoplasm and shows greater variations in the free water in the tissues and in the lymph stream. The total water content in the body is, however, constant from day to day under uniform conditions.

Water in the organism moves continually; excretion through the kidneys is continuous, similarly through the lungs, through the skin and through the intestines. The water so lost is made up from free water of the tissues. There is thus a *continuous movement* of water from the tissues to the blood stream. Water is continually taken in to make up for the water lost.

What happens when water is ingested into the alimentary tract?

III. Water taken into the alimentary tract is absorbed into the blood stream in the form of an isotonic solution. The ingestion of water thus starts a series of changes in the body, beginning with the movement of salt to convert the water into an isotonic solution, and followed by the absorption of water into the blood stream. The changes that occur after absorption have been studied by numerous observers who investigated the changes in the water content of the blood and of the various organs and tissues. The most noteworthy studies in this direction are those of Marx.³ He made numerous hemoglobin determinations with an exact hemoglobinometer before and after drinking 50 to 2000 cc. of water or weak tea. He found that after drinking there is always a reduction in the hemoglobin in the first twenty to forty minutes. This initial dilution is followed in fifty to eighty minutes by an increase in the concentration of the hemoglobin to the original figure. This is followed by a second dilution, which is less steep than the first, but lasts longer. In about four to five hours the original fasting value is reached.

Marx also found that the initial dilution is not proportional to the fluid intake. In many of his observations there was an equal dilution whether the fluid intake was a 1000, 500, 125 or 50 cc. The dilution could not therefore be explained by the amount of the ingested water. It was necessary to assume that the ingested water, whether large or small, started complicated exchange processes between the blood and the tissues. Marx even obtained the same curve of blood dilution when the drinking of water was suggested to an individual in hypnosis.

IV. While this dilution of the blood stream is going on the ingested water is absorbed from the alimentary tract into the blood stream. The excess of water is eventually eliminated through the kidneys but diuresis does not begin until about fifty to sixty minutes later and is prolonged over hours. Meanwhile the water has left the blood stream and has passed into the tissues. It is necessary that we know where this water goes to.

Studies of the water content of organs and tissues have been made by Magnus,⁴ Engels,⁵ Wahlgren,⁶ Tashiro,⁷ Baer,⁸ and others. It has been definitely shown that the water leaving the blood stream is taken up by various organs, especially the muscles and the skin, and particularly the connective tissue of these organs. The free water there is thus increased and we have in the muscles and the skin depots which the organism makes use of to store any excess of water. The living muscle of a rabbit showed an increase in weight after the ingestion of water and a diminution in weight after the abstraction of water by means of the intravenous injection of hypertonic salt solutions.

In addition to the muscles and the skin, another organ is concerned in the taking up of water, namely the liver. It has been shown by Lamson and Roca⁹ and by Pick and his associates,¹⁰ that the liver easily takes up fluid temporarily and acts as a reservoir. In a dog with an Eck fistula, that is, one in which the greater part of the liver is excluded from the circulation, the ingested water begins to appear in the urine in from twenty to thirty minutes, while in the animal with the liver intact it appears in from fifty to sixty minutes.

The spleen as a reservoir for the blood has been considered by Barcroft.¹¹

The liver, muscles and skin thus take up the ingested water, and after a period the excess of water in the depots gradually flows back into the blood stream to be excreted by the kidneys. Excretion continues until all the excess is removed and the mean normal is retained.

The organs mentioned, namely, the muscles, skin, liver and kidneys, form a group of effector organs among whose functions there is also that of taking up the excess of water and gradually eliminating it from the body. There is a continuous movement of water

from the alimentary canal into the blood stream, into the water depots, back again into the blood stream, to be eliminated by the kidneys and extrarenally by the lungs, the skin and the intestinal tract.

These organs form thus a unitary mechanism and their function as far as the taking up and giving off of water is concerned, must be considered as a unit. Water moves in these organs to and from the blood stream, through tissues and membranes which form barriers, and through which it moves at varying rates of speed.

In connection with the water content of these organs the sodium chlorid content must be considered. When an excess of salt is taken in, it is absorbed into the blood stream and from there wanders into certain depots, chief of which are the muscles and the skin. Water is retained with the salt, and whenever water moves in the body it does so in the form of a saline solution. When there is an excess of salt in the tissues an extra amount of water is retained. A change in the rate of movement of sodium chlorid necessitates also a change in the rate of water movement.

V. The organs mentioned above, namely, the muscles, skin, kidneys and also the liver, constitute a mechanism for the maintenance of the normal water content of the internal milieu. As they constitute the effector organs in the maintenance of a vegetative function they must be coördinated in an exact manner. The exact coördinated action of such a mechanism, the effector organs of which are so widely distributed throughout the body, can only be attained by means of the central nervous system. This was the understanding of Claude Bernard. It is a fundamental principle of physiology, that every vegetative function necessitating the maintenance of a constant value has a central coördinating regulation. We may accept as fundamental that such regulation is effected, first peripherally, that is, in the effector organs themselves, by means of a physicochemical system; second, centrally, by means of the vegetative nerves presided over by a center in the brain; third, by means of hormones. Every complicated vegetative function is regulated in this manner and we can only have a full understanding of such a function when we have a full understanding of the manner in which it is regulated.

In the peripheral effector organs the particular function is performed in the colloidal system of the protoplasm. The performance of the function is dependent upon the distribution of the electrolytes in the phases of the colloidal system. A change in the distribution of the electrolytes means a change in the character or intensity of the function, either an increase in function or a decrease. Of the electrolytes concerned we know that hydrogen, hydroxyl, calcium, sodium and potassium are especially important. We also know that antagonistic influences are exerted by hydrogen and hydroxyl ions, also by calcium on the one hand and sodium and

potassium on the other. Other electrolytes such as magnesium, iron, sulphate and phosphate are also of importance, but we may take the first named as the best known in their action.

These problems have been studied especially in the school of Kraus, and those who are interested in them will find a careful consideration of the functions of the electrolytes in physiologic processes in the work of Zondek.¹²

Kraus and Zondek have come to the conclusion that the influence of the vegetative nerves on the colloidal system of the cell is through the electrolytes. The two antagonistic nerves, namely, the sympathetic and the parasympathetic, exert their influence by changing the distribution of electrolytes in the colloidal system of the protoplasm. Their influence on the function of the cell is therefore identical with that of certain electrolytes, and their antagonism to one another is dependent upon the antagonistic influence of certain electrolytes. The influence of the sympathetic nerve is identical with that of calcium, and the influence of the vagus with that of potassium. Kraus and Zondek speak, therefore, of the vegetative system, including under this term the vegetative nerves, their centers in the brain, and the electrolytes in the periphery which they influence. The vegetative system changes the function of the effector organs either by increasing the rate at which the individual function is performed or by diminishing the rate.

As the change in the rate at which a function is performed in the cell can only be produced by a change in the electrolytes, it is evident that the action of drugs or poisons must also be on the electrolytes. The action of certain drugs on the cells is therefore identical with the action of the nerves, and the antagonistic influences of certain drugs on the function of the cell is identical with the antagonistic action of the electrolytes and of the vegetative nerves. Hormones produced in the body are such drugs and their influence on certain cells is therefore identical with the influence of nerves and electrolytes on the cell. The identical action of adrenalin, of the sympathetic nerves fibers and of calcium is well known. Such hormones serve as a third means of regulating the rate of function of the effector cells and organs.

To us it is of interest to know how the function of the effector organs concerned in the water exchange is regulated in this three-fold manner, by means of electrolytes at the periphery and centrally by the vegetative nerves and by certain hormones.

VI. We have considered the effector organs for the water exchange in the body, namely, the muscles, skin, kidneys and liver as a unitary mechanism which has as its function the maintenance of the normal water content of the body and especially of the blood stream. Water moves continuously through these organs, and the rate of motion is dependent upon the intake of water and upon the control exercised on the rate of motion. It is obvious that when

the rate of motion of water in one of these organs is either increased or diminished, the rate of motion in the other organs of this mechanism must also be increased or diminished. Otherwise the water content of the blood will rapidly become increased or diminished.

What influences the rate of motion of water locally? Water moves from its depots to the blood stream through barriers made up of layers of tissues. Reid¹³ long ago and, more recently, Wertheimer¹⁴ and Mond,¹⁵ among others, have studied the passage of water through many-layered living membranes. It was found that water does not move through a living membrane of many layers in the same manner as it does through a dead membrane. In the living membrane the rate of water through it and the degree of permeability for water on one side or the other, is dependent upon the electrolytic content of the water and upon the ability of the individual layers to take up water; the latter again is dependent upon the electrolytic content of the individual layers. These investigations show that the permeability of the living membrane and the rate of water through it can be influenced by a change in the electrolytic content of the water.

Here we have experimental evidence as to the manner in which the rate of movement of water from their depots to the blood stream is affected, namely, by a change in the distribution of the electrolytes. This is the peripheral physicochemical regulation of water movement in the body. It is obvious that when a change in rate of water movement is produced in some part of the mechanism for water exchange, a corresponding change of rate must be produced in the other parts. Such a corresponding change can only be effected through a central nervous regulation. Wertheimer¹⁴ has also shown that the water content of muscle tissue can be influenced by the vegetative nerves. In accordance with the view that vegetative functions are controlled by the vegetative system, we must assume such a regulating control by the vegetative nerves on the electrolytes of the tissue membrane barriers through which water moves. It is also clear that we must look for a center in the brain for the seat of such central regulation.

It is unnecessary to enter here into the details of all the experiments concerned. From the time of Claude Bernard investigators have busied themselves with the study of the central regulation of water exchange especially in connection with diabetes insipidus. Through the work of Eckhard,¹⁷ Aschner,¹⁸ Camus and Roussy,¹⁹ Houssay,²⁰ Leschke,²¹ Bailey and Bremer,²² Curtis,²³ Pohle,²⁴ Jungmann and Bernhardt,²⁵ and numerous others, it has been definitely established that in the hypothalamus, in the gray matter surrounding the third ventricle, a center is situated which influences the rate of water movement through the tissues and kidneys. Increase in the rate of water movement can be produced by injury to this center. A change in water movement resulting in a slower rate

from the tissues to the blood stream than in the opposite direction has also been produced. It is clear that when the water movement from the tissues to the blood stream is slower than the movement of water in the opposite direction that the continuous intake of water must result in an accumulation of water in the tissues.

It is important to keep in mind that this center is situated in that portion of the gray matter which contains centers for numerous vegetative functions, perhaps for all. It contains centers for the regulation of salt in the body, for the rate of metabolism, for the regulation of carbohydrate, fat and protein metabolism, for respiration, circulation, blood pressure, uterine contraction and for other functions.

So much for the second mode of regulation, that is, by means of the nervous system.

VII. The third mode of regulation—that by means of hormones—also occurs. There are especially two hormones whose effect on the water exchange is well known, that of the thyroid gland, and that of the posterior lobe of the hypophysis. Eppinger²⁶ has studied the action of the thyroid gland on the water exchange and has shown that its effect is to increase the rate of water movement. Part of this action is due to the increase in the metabolic rate and part of it is probably due to its effect on the separating membranes through which water moves.

Of greater importance is the effect of the hormone of the posterior lobe of the hypophysis. This gland is in close relation with the hypothalamus and its centers, and there is probably a reciprocal influence on the gland and on many of the centers in this region. The influence of this hormone on the rate of water movement has been studied by Magnus and Schafer.²⁷ Schafer and Herring,²⁸ and by Abel and his associates;²⁹ its influence on the capillaries has been studied by Krogh and his associates.³⁰ The influence of this hormone on the rate of water movement is definitely shown in the slowing of water movement through the tissues after its administration in cases of diabetes insipidus. In accordance with the Kraus-Zondek conception of the action of drugs and hormones on the distribution of the electrolytes in the colloidal system of the protoplasm we must assume that the hormone of the posterior lobe of the hypophysis exerts its action on the physicochemical mechanism in the tissue membranes through which water moves by changing the electrolytic distribution there, and with it producing a change in the rate of water movement.

VIII. We have thus come to consider the mechanism which regulates the water exchange in the body as consisting of the following elements: (1) A regulating center in the interbrain closely connected with the centers for the regulation of sodium chlorid metabolism, other mineral exchange, protein, carbohydrate and fat metabolism, and other vegetative centers; (2) reservoir organs which take

up any excess of water from the blood, namely, the muscles and skin, especially their connective tissue, the liver, and possibly also the spleen; (3) barriers to the blood stream consisting of membranes in the tissues and the walls of capillaries through which the stream of water is regulated; (4) excretory organs, chief of which are the kidneys, but in addition the lungs, the skin and the intestines through which water is eliminated. All these organs, especially the connective tissue of the muscles and the skin, and the kidneys, constitute a functional unit regulated by the center.

Such regulation we conceive to be effected in the following manner: Water absorbed from the alimentary tract produces a change in the water content of the blood. The cells of the center in the hypothalamic region react to this change in the water content and respond with impulses to the organs constituting the functional unit to counteract the change in the water content of the blood. The impulses reach these organs by way of the vegetative nerves. In addition to this nervous regulation the functional mechanism is under the continuous influence of the internal secretions of certain glands, chief of which are the intermediate and posterior lobes of the hypophysis. This gland again is under the regulating influence of the center in the hypothalamus.

The internal secretion of this gland as well as the vegetative nerves, affect the individual organs of the functional mechanism for water regulation through the electrolytes in the individual cells and through changes in the colloidal system of the cell. The change in the electrolytes is a change in the relation of certain electrolytes to one another and a change in concentration of the hydrogen and hydroxyl ions. With these changes there is a change in the intensity of the function of the cell and a change in the rate of the water movement.

The object of this whole mechanism is to maintain the normal water content of the organism, and especially the water content and volume of the blood. The latter is of paramount importance. A change in the intensity of the function of one organ of this mechanism must necessarily involve a corresponding change in the other organs if the object of the whole functional mechanism is to be maintained. The consideration of one organ of this mechanism as a separate entity entirely distinct of the others is therefore not possible. Nor can we consider the function of an organ of this mechanism apart from its regulating center and from the nervous impulses from this center. The consideration of changes in the electrolytes in a particular organ of this mechanism, whether the connective tissue of the skin and muscles, the capillaries, or the kidneys alone, without considering them as being continuously influenced by impulses from a center, is not permissible.

IX. With this conception of the manner in which the movement of water through the body is regulated we may consider the problem

of edema. We mean by edema the accumulation of fluid in the skin and subcutaneous tissue in such a manner that the fluid can be easily displaced by pressure on the skin, leaving a depression which soon disappears with the return of the displaced fluid. The fluid which has accumulated in the skin and subcutaneous tissue is not a part of the colloidal system of the protoplasm, but is an augmentation of the free fluid which is normally present between the colloidal systems and between the cells. This free fluid can be increased to a considerable degree without becoming noticeable except for the increase in weight, but when 5 to 6 liters have accumulated as free fluid in the various water depots, this becomes visible as edema. The questions we meet with are, first, how does it happen that so much water accumulates in the depots? and second, why does not the water move toward the blood stream to be excreted?

We know that the water from the depots can move toward the blood stream at various rates of speed. When water is ingested the mechanism for water exchange acts at once, the ingested water goes from the blood stream into the tissues, returns to the blood stream and is excreted by the kidneys. When much water is ingested the rate of movement of the water is rapid; when no water is ingested, the rate is slow. This is shown by the urine output, which is increased in the first case and diminished in the second. The blood volume remaining within normal limits in either case, the excess of water to be excreted must move at a greater rate. When, as in edema, water persists in the depots, the rate of movement through the tissue barriers to the blood stream is evidently diminished. We have said that the rate of movement of water through such barriers is dependent upon the electrolytic constellation in them. We must assume then that a change has occurred in the physicochemical regulation, that is, in the distribution of electrolytes in the tissue barriers where the rate of water movement is diminished. When the fluid keeps coming into the depots at the regular rate of flow, but the rate of flow from the depots to the blood stream is diminished, the free water in the depots must necessarily be increased. When the increase has reached a certain degree the water becomes visible as edema.

We must therefore consider general edema, that is, the accumulation of free fluid in the water depots of the body to a visible extent, as the result of a discrepancy between the more rapid rate of movement of water from the blood to the tissues and the slower rate of movement in the opposite direction. Whenever such a discrepancy occurs edema must necessarily result.

Edema results also in some local area alone when such an area is inflamed, such as occurs in local myositis or cellulitis. In this case the local discrepancy in the rates of water movement can be assumed to be due to a local change in the electrolytes in that areas as a result of the inflammation.

When the edema is general such as occurs in cardiac failure, in acute nephritis, or in chronic starvation, the diminution in the rate of water movement over the entire body must be the result of a change in the electrolytic distribution in the entire peripheral mechanism for water exchange, namely, the muscles, skin, liver and kidneys. Such a widespread change involving the entire mechanism could possibly be produced by a toxic substance which circulates in the blood stream and thus reaches the entire mechanism. This is perhaps the case in the edema found in a generalized myositis, in the edema which occurs in trichinosis, in the edema which sometimes occurs in arsenic poisoning, and in that of experimental uranium poisoning. But we know of no poison circulating in the blood stream which may affect all the tissues in cases of edema of cardiac failure, of renal disease, or of chronic undernutrition. Here we must assume that a change in the electrolytes responsible for the slowing in the rate of water movement is produced reflexly by way of the central nervous control acting through the vegetative nerves or through hormonal influences, or in both ways. In diabetes insipidus such a general change produced by the regulatory center results in an increase in the rate of water movement. It is, therefore, easy to understand that a change of regulation in the opposite direction would produce a slowing in the rate of water movement. If there is thus a discrepancy between the rate of flow to the tissues and the rate of flow from the tissues, a generalized edema must result after a certain amount of water has accumulated.

X. The question which confronts us now is: under what conditions is such a regulatory change in the mechanism brought about? We have said that the organism has means of maintaining the constancy of the internal milieu. It is particularly the volume and water content of the blood which the organism continuously maintains within certain limits and which vary but slightly even in pathologic conditions. If the mechanism we have discussed serves such a purpose then it must come into play whenever the normal water content of the blood is endangered. This is actually what occurs. We know that when the body is deprived of water all the free water in the tissues will be drained into the blood stream before the blood begins to lose its water, while at the same time the kidneys shut down to prevent any loss of water through them, even to complete anuria. In severe diarrheas, such as occur in cholera, the tissues become completely dry and anuria results in an attempt on the part of the organism to keep the water in the blood.

The opposite also occurs. Under certain conditions there is danger that the water content of the blood will become unduly increased. If the mechanism for the regulation of water exchange is to fulfill its purpose it must immediately regulate the rate of water movement to the blood stream in such a manner that an undue increase in the water content of the blood is prevented. The conditions in which

such a threatened increase in the water content of the blood occurs are cardiac failure and acute diffuse nephritis.

In cardiac failure there is a slowing of the blood stream and the blood accumulates in the venous system. As the blood accumulates it is taken up by the various organs, which become passively congested. A great deal of blood can be removed in this manner by the liver, the spleen and the capillaries of the skin. The importance of the latter has been shown by Wollheim.³¹ The kidneys also become congested and the glomeruli are filled with blood. The result of glomerular overfilling is a diminution in the flow of blood through them, a diminution in the output of urine and, of course, a diminution in the excretion of water. When the limit of congestion is reached, then the mechanism for water exchange must come into play and adapt the rate of water movement from the tissues to the blood stream to the rate with which it leaves the body through the regular channels, so that the water content of the blood is maintained within the normal limits.

Impulses reaching the central regulation of the mechanism for water exchange cause reflexly, by way of the nerves or hormones, or both, a change in the electrolytic distribution throughout all the effector organs of the mechanism. The result is a slowing in the rate of water movement through the tissue barriers to the blood stream. As the intake of water remains normal and is quickly removed after ingestion, the free water in the depots is quickly increased and soon becomes visible as edema.

In acute diffuse nephritis there is also danger that the water content of the blood may become unduly increased. In this disease all the glomeruli of both kidneys are affected. They are filled with an exudate consisting of leukocytes and endothelial cells, and with a hyaline plasma. Practically no red blood corpuscles pass through them and, depending upon the severity of the inflammation, a more or less thin trickle of plasma passes through the capillaries of the glomeruli. The result is a diminution in the output of urine and, of course, of water. The water content of the blood would necessarily increase if the water kept moving through the tissues at the same rate of speed as before. The blood volume, however, remains normal. We must therefore assume that there is a slowing in the rate of water movement from the depots to the blood stream corresponding to the rate with which water is lost from the body through the diseased kidneys and through the extrarenal channels. There is therefore produced reflexly through the central regulation a generalized change in the electrolytic distribution in all the tissue membranes through which water moves. Water taken in as usual is quickly removed to the depots. The diminution in the rate of removal from the depots results in an increase there in the free water, which soon appears as edema.

Thus we have two conditions in which a threatened increase in

the water content of the blood is prevented by the proper adaptation of the mechanism for water exchange. Such an adaptation can only be brought about through a central regulation.

In this connection it is important to remember the influence of the sodium chlorid content of the free water in the depots. Sodium chlorid passes from the blood to the tissues and in the opposite direction in solution. It is clear that when the rate of water movement is diminished the rate of movement of sodium chlorid is also diminished. When edema occurs, the salt contained in the food, absorbed into the blood stream, and passed into the tissues, is prevented from returning to the blood stream by the slowing in the rate of water flow. As its concentration increases it draws more water to it and thus helps to increase the extent of the edema.

We have so far assumed that the volume and water content of the blood remain within the normal limits in both the conditions where the mechanism for water regulation prevents an undue increase. That the blood volume is actually within the normal limits has been shown by the studies of Bock,³² Linder, Lundsgaard, van Slyke and Stillman,³³ Seyderhelm and Lampe,³⁴ Schmidt,³⁵ Brown and Rowntree.³⁶

XI. We have so far made an attempt to explain the edema which appears when the constancy of the water content of the internal milieu is threatened. There occur, however, excessive accumulations of water in the tissues when the constancy of the water content of the internal milieu is not threatened. Such accumulations of water are seen in the edema of chronic undernutrition, of severe diabetes, in chronic wasting disease and in myxedema. In all these conditions the water content of the blood is not disturbed, actually it is within the normal limits, and yet the rate of water movement from the tissues to the blood has become slower compared to the rate of flow of water from the blood stream to the tissues. For only through such a discrepancy can a sufficient amount of free water accumulate in the tissues to become visible as edema. As the edema is general, there must have occurred a change in the whole mechanism for water movement, and, as we have said before, such a general change must occur through the central regulatory mechanism. We know of no toxic substance which circulates in the blood in chronic undernutrition and which may produce a change in the barrier membranes without the intervention of the central regulatory control. Evidently, for some reason, such a change does occur. Under what conditions is it brought about?

When we examine the diseases mentioned, namely, chronic undernutrition, wasting diseases, severe diabetes with edema and myxedema, we find certain factors common to all. In all of these there is a diminution in intensity in a number of vegetative functions. There is a diminution in the state of nutrition and in the basal metabolic rate. Typical is the state of chronic undernutrition as

it was observed in the cases of war edema. We find here a diminution in the metabolic rate, in the blood pressure, in the pulse rate, in the amount of protein in the blood, even in the body temperature. There is thus a diminution in rate in a number of vegetative functions. Physiologically a decrease in practically all vegetative functions occurs periodically in the hibernating animal. Basal metabolic rate, circulation, blood pressure and respiration rate, are all diminished during hibernation. Urination practically ceases and the rate of water movement through the tissues is at a minimum. We know that all these vegetative functions have a central control in the nervous system and it is difficult to see how such a general lowering of all the functions can be brought about in the hibernating animal except through the intervention of the central regulatory apparatus.

It is therefore logical to assume that the depression of a number of vegetative functions in chronic undernutrition is similarly brought about by changes in the regulatory control. The purpose is the conservation of the chronically undernourished organism. Lusk³⁷ points out that the reduction in the basal metabolism in chronic undernutrition affords a factor of safety for the conservation of the body.

We may now take a step further and logically assume that with such a regulatory change in other vegetative functions there is also a regulatory change in the rate of water movement. This, like the rate of other functions has become slower. The slowing is particularly seen when an extra load of water and salt is given. Jansen,³⁸ and Schittenhelm and Schlecht³⁹ studied the cases of war edema. From their studies it is evident that when large amounts of water and salt are given to cases of chronic undernutrition there is evidence of a diminution in the rate of water movement from the tissues to the blood stream. With the intake of large amounts of water and salt which promptly move into the water depots, there is an increase in the free water there which soon appears as edema.

Our conception then of the formation of edema in chronic undernutrition—and that includes the undernutrition due to a faulty diet, that of severe diabetes, and of chronic wasting diseases—is as follows: with the progress of the undernutrition there is a depression of many of the vegetative functions as a result of central regulatory influences. Water movement through the body, being a vegetative function the central regulation of which is closely associated with that of other fundamental functions, especially with that of metabolism, is similarly depressed. As the water content of the blood remains within the normal limits, the intake of large amounts of water and salt is necessarily followed by an increase in the amount of water in the tissues which soon becomes visible as edema.

XII. In addition to the forms of edema which we have discussed there occur cases of edema without any apparent cause, that is, without any cardiac failure or renal disease, and without chronic undernutrition. I have seen several such cases and have reviewed the reported cases elsewhere.⁴⁰ The cases, especially those which have been studied more thoroughly, seem to have certain things in common. None of these patients suffered from any cardiac or renal affection or from chronic undernutrition which would cause edema. They all had edema which was more or less generalized, with a diminution in the urinary output. In those cases which were properly studied there was a diminution in the free hydrochloric acid of the stomach or a total absence of it, a more or less normal output of an added amount of water, and a retention and delayed excretion of an added amount of sodium chlorid. In some cases there was also a diminution in the protein content of the blood plasma. There are no studies recorded concerning the blood volume in these cases, but we are probably correct if we assume that the blood volumes were within the normal limits.

We may, therefore, agree with the authors of these reports that the edema is the result of a disturbance in the sodium chlorid exchange. The rate of movement of sodium chlorid through the tissues and membranes is diminished. The diminution in the rate of movement affects the sodium chlorid in all the regions of the body and is therefore most likely to be the result of a disturbance in the center of regulation.

XIII. With this conception of edema the directions for its treatment stand out clearly. The treatment of the fundamental disease of which edema is the symptom comes first. This is the case in cardiac failure. In acute diffuse nephritis we have no means to influence the pathologic process in the kidneys directly.

When we come to treat the symptom of edema, there are certain principles which we can follow:

1. To diminish the intake of water below that of the output, no matter how small, as long as there is no anuria. When the intake is diminished below the output the water lost from the blood must be made good from the water in the tissues if the blood volume is to remain normal.

2. The total or almost total elimination of sodium chlorid from the food. The loss of sodium chlorid from the blood by way of the urine must be made good from the salt in the tissues which passes into the blood stream and takes water with it.

There are no direct means of influencing the regulatory center for water exchange itself. But when this is primarily responsible for the slowing in the rate of water movement the basal metabolic rate also is usually slowed, as in chronic undernutrition. When the basal metabolic rate is increased the rate of water movement is also increased. We have then,

3. To stimulate the rate of oxidative processes in the cells whenever it is found to be diminished.

For this purpose we have two means at hand: first, a proper diet, especially rich in protein, such as has been suggested by Epstein⁴¹ in cases of lipoid nephrosis; and second, the hormone of the thyroid gland, which has been introduced into the treatment of edema by Eppinger.²⁶

When, in spite of the limitation of water and salt intake, the edema cannot be controlled we have at our disposal diuretics as follows:

The purine substances, *cafein*, theobromin, theophyllin, and their derivatives.

The mercury compounds, calomel, novasurol and salyrgan.

Calcium chlorid and ammonium chlorid.

Urea.

The action of the purine derivatives and of the mercury compounds we assume to be on the kidneys and on the tissue barriers through which water moves. In accordance with our ideas concerning the similarity of the action of drugs and poisons and of nerves on the electrolytes of the colloidal system of the protoplasm, it is logical to assume that the action of these drugs is on the tissue barriers through which water moves. In all probability a change in the electrolytes of the tissues is brought about by these drugs, the result of which is an increase in the rate of water movement through them. It is clear that these drugs should not be used when an acute inflammatory exudate blocks the glomerular capillaries through which the excess of water must be removed.

The diuretic action of the acid-producing salts, such as calcium chlorid and ammonium chlorid, is due to the excess of acid radicals in the body, which must be excreted in solution, and the excretion thus carries with it a certain amount of water.

The diuretic action of urea is primarily in the kidneys, and is due to its not being reabsorbed in the tubules; it thus prevents a certain amount of water from being reabsorbed. Whether it also has an effect on the tissues is not known.

Summary. We have thus come to the understanding that in every case of general edema there is a slowing up in the rate of movement of water from the depots through the tissue barriers to the blood stream. With the normal water and salt intake and their rapid removal from the blood into the tissues, the free water there is rapidly increased. When a certain amount of water has accumulated it becomes visible as edema. The slowing is the result of a central regulatory change and affects the constellation of electrolytes in the tissue barriers through which the water moves to the blood and lymph streams. This slowing is produced, first, whenever the water content of the blood threatens to be unduly increased, as in cardiac failure, or in acute diffuse nephritis; second, when the

change is primarily in the regulatory center, along with the depression of other vegetative functions, especially of the basal metabolic rate. This is the case in chronic undernutrition and in chronic wasting disease. Third, when there is a primary disturbance in the central regulation for the control of sodium chlorid in the body. This is the case in certain cases of edema without cardiac or renal diseases, and without chronic undernutrition.

REFERENCES.

1. Haldane, J. S.: *The New Physiology, The Harvey Lectures, Series XII*, J. B. Lippincott Company, 1916-1917, p. 25.
2. Bernard, Claude: *Leçons sur les phénomènes de la vie*, Paris, 1878, 1, 113.
3. Marx, H.: Untersuchungen über den Wasserhaushalt (I Mitteilung), *Die Blutberdünnung nach Flüssigkeitsaufnahme*, *Klin. Wchnschr.*, 1925, 4, 2339. Untersuchungen über den Wasserhaushalt (II Mitteilung); *Die psychische Beeinflussung des Wasserhaushaltes*, *Klin. Wchnschr.*, 1926, 5, 92. Untersuchungen über den Wasserhaushalt (III Mitteilung): *Über die Austauschvorgänge zwischen Blut und Gewebe bei Gesunden und Kranken*, *Deutsch. Arch. f. klin. Med.*, 1926, 152, 354.
4. Magnus, R.: *Über die Veränderung der Blutzusammensetzung nach Kochsalzzufusion und ihre Beziehung zur Diurese*, *Arch. f. exper. Pathol. u. Pharmacol.*, 1900, 44, 68.
5. Engels, W.: *Die Bedeutung der Gewebe als Wasserdepots*, *Arch. f. exper. Pathol. u. Pharmacol.*, 1904, 51, 346.
6. Wahlgren, W.: *Über die Bedeutung der Gewebe als Chlordepots*, *Arch. f. exper. Pathol. u. Pharmacol.*, 1909, 61, 97.
7. Tashiro, N.: *Über Änderungen im Wassergehalte der quergestreiften Muskulatur als Folge der Störungen des Wasserhaushaltes von Kaninchen*, *Naunyn-Schmiedeberg's Arch. f. exper. Pathol. u. Pharmacol.*, 1926, 111, 218.
8. Baer, B.: *Über die Bedeutung der quergestreiften Muskulatur für die Regelung des Wasserhaushaltes bei peroraler Wasser- und Salzdarreichung*, *Naunyn-Schmiedeberg's Arch. f. exper. Pathol. u. Pharmacol.*, 1927, 119, 102.
9. Lamson, P. D. and Roca, J.: *The Liver as a Blood Concentrating Organ*, *J. Pharmacol. and Exper. Therap.*, 1921, 17, 481.
10. Pick, E. P.: *Wasser- und Mineralstoffwechsel in ihren Beziehungen zu Verdauungs- und Stoffwechselkrankheiten*, *Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkrankh.*, 1927, 6, 125.
11. Barcroft, J.: *Some Recent Work on the Function of the Spleen*, *Lancet*, 1926, 210, 544.
12. Zondek, S. G.: *Die Electrolyte*, Julius Springer, Berlin, 1927.
13. Reid, E. W.: *Transport of Fluid by Certain Epithelia*, *J. Physiol.*, 1900-1901, 27, 436.
14. Wertheimer, E.: *Über irreziproke Permeabilität*, *Pflüger's Arch. f. d. ges. Physiol.*, 1923, 199, 383; *Über die Quellung geschichteter Membranen und ihre Beziehung zur Wasserwanderung*, *Pflüger's Arch. f. d. ges. Physiol.*, 1925, 208, 669; *Weitere Untersuchungen an lebenden Membranen*, *Pflüger's Arch. f. d. ges. Physiol.* 1925, 210, 527.
15. Mond, R.: *Untersuchungen am isolierten Dünndarm des Frosches*, *Pflüger's Arch. f. d. ges. Physiol.*, 1924, 206, 172.
16. Hoffmann, A., and Wertheimer, E.: *Eine nervöse Regulation im Wasserhaushalt*, *Pflüger's Arch. f. d. ges. Physiol.*, 1927, 217, 138.
17. Eckhard, C.: *Zur Deutung der Entstehung der vom vierten Ventrikel aus erzeugbaren Hydrurie*, *Ztschr. f. Biol.*, 1903, 44, 407.
18. Aschner, B.: *Über die Funktion der Hypophyse*, *Pflüger's Arch. f. d. ges. Physiol.*, 1912, 146, 1.
19. Camus, J. and Roussy, G.: *Hypophysectomie et polyurie expérimentales*, *Compt. rend. Soc. de biol.*, 1913, 75, 483; *Polyurie expérimentale permanente (Diabète insipide)*, *Compt. rend. Soc. de biol.*, 1920, 83, 764.
20. Houssay, B. A.: *Aur la polyurie soidisant hypophysaire*, *Compt. rend. Soc. de Biol.*, 1918, 81, 381.
21. Leschke, E.: *Beiträge zur klinischen Pathologie des Zwischenhirns*, *Ztschr. f. klin. Med.*, 1919, 87, 201.

22. Bailey, P. and Bremer, F.: *Experimental Diabetes Insipidus*, Arch. Int. Med., 1921, 28, 773.
23. Curtis, G. M.: *The Production of Experimental Diabetes Insipidus*, Arch. Int. Med., 1924, 34, 801.
24. Pohle, E.: *Einfluss des Nervensystems auf die Osmoregulation der Amphibien*, Pfleger's Arch. f. d. ges. Physiol., 1920, 182, 215.
25. Jungmann, P. and Bernhardt, H.: *Experimentelle Untersuchungen über die Abhängigkeit der Osmoregulation von Nervensystem*, Ztschr. f. klin. Med., 1924, 99, 84.
26. Eppinger, H.: *Zur Pathologie und Therapie des menschlichen Ödems*, Julius Springer, Berlin, 1917.
27. Magnus, R. and Schafer, E. A.: *The Action of Pituitary Extracts upon the Kidney*, J. Physiol., vol. 27, Proc. Physiol. Soc., 1901, p. ix.
28. Schafer, E. A. and Herring, P. T.: *The Action of Pituitary Extracts upon the Kidney*, Proc. Roy. Soc. London, Series B., 1906, 77, 571.
29. Abel, J. J.: *Physiological, Chemical and Clinical Studies on Pituitary Principles*, The Harvey Lectures, Series XIX, J. B. Lippincott Company, 1923-1924, p. 154.
30. Krogh, A.: *The Anatomy and Physiology of the Capillaries*, New Haven Press, New Haven, 1922.
31. Wollheim, E.: *Zur Funktion der subpapillären Gefäßplexus in der Haut*, Klin. Wchnschr., 1927, 6, 2134.
32. Boek, A. V.: *The Constancy of the Volume of Blood Plasma*, Arch. Int. Med., 1921, 27, 83.
33. Linder, G. C., Lundsgaard, C., Van Slyke, D. D., and Stillman, E.: *Changes in the Volume of Plasma and Absolute Amount of Plasma Protein in Nephritis*, J. Exp. Med., 1924, 39, 921.
34. Seydewitz, R. and Lampe, W.: *Die Blutmengenbestimmung und ihre klinische Bedeutung*, Ergebn. d. inn. Med. u. Kinderheilk., 1925, 27, 245.
35. Schmidt, W.: *Blutmengen-Bestimmungen bei Nieren- und Herzkrankheiten*, Ztschr. f. d. ges. exper. Med., 1927, 58, 276.
36. Brown, G. E. and Rowntree, L. G.: *Blood Volume in Edema of Glomerular Nephritis and Nephrosis*, Arch. Int. Med., 1928, 41, 44.
37. Lusk, G.: *The Physiological Effect of Undernutrition*, Physiol. Rev., 1921, 1, 523.
38. Jansen, W. H.: *Die Ödemkrankheit*, Deutsch. Arch. f. klin. Med., 1920, 131, 144.
39. Schittenhelm, A. and Schlecht, H.: *Die Ödemkrankheit*, Julius Springer, Berlin, 1919; reprinted from Ztschr. f. d. ges. exper. Med., 1919, 9, 1.
40. Elwyn, H.: *Edema and Its Treatment*, p. 130, The Macmillan Company, New York, 1929.
41. Epstein, A. A.: *Concerning the Causation of Edema in Chronic Nephrosis*, Am. J. Med. Sci., 1917, 154, 638.

GASTRIC HEMORRHAGE DUE TO FAMILIAL TELANGIECTASIS.

BY L. NAPOLEON BOSTON, A.M., M.D.,

PROFESSOR OF MEDICINE, WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA; PROFESSOR OF PHYSICAL DIAGNOSIS (GRADUATE SCHOOL), UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

A CURSORY survey of the literature disclosed records of 3 cases of recurrent rectal hemorrhage, one of oral bleeding and one of hematemesis, which had been accompanied by cutaneous telangiectases. Wilson¹ gave us the first recorded instance of rectal bleeding from telangiectases in 1896; Fox² recorded a case in 1908, where recurrent rectal hemorrhage was an annoying symptom; Phillips³ in 1908

cites the case of an extensive telangiectasis of the skin and mucous surface of the mouth with hemorrhages from the pharynx, and possibly from the stomach. Hutchinson and Oliver's⁴ patient experienced recurrent rectal hemorrhage and hemorrhage from other mucous membranes; and Pringle⁵ in describing his case alludes to recurrent attacks of vomiting blood. Gastric hemorrhage, in the absence of pain and other gastrointestinal symptoms, has been the outstanding clinical feature in the 3 case records here delineated.

Familial epistaxis and familial telangiectasis are terms seldom used but known to otolaryngology; whereas telangiectasis has not been employed in connection with painless hemorrhage of either gastric or rectal origin.

The 3 private cases furnishing the clinical subject matter for this report, each had telangiectases of the skin and mucosæ, as well as recurrent hemorrhages from both the stomach and the rectum. One of these patients was studied at laparotomy and another died from gastric hemorrhage. In each instance the history indicated other members of the same family, or near relatives who had experienced similar attacks of bleeding from mucous surfaces. The familial etiologic nature of the disease is evidenced in the report of my cases, and in all records cited from the literature.

Painless gastric hemorrhage, calls for a careful inquiry regarding the existence of recurrent mucous bleedings among other members of the family. Moreover, persons suffering from recurrent epistaxis may also bleed from other mucous membranes.⁶

Characteristic of familial gastric and rectal hemorrhage are: (a) the blood clotting time is within normal limits; (b) the number of blood platelets per cubic millimeter varies between 250,000 and 400,000; (c) following large hemorrhages, the blood findings are those of secondary anemia, while nucleated red blood cells are occasionally present; (d) patients recover rapidly following seemingly large hemorrhages; (e) cases do not bleed extraordinarily after surgical operations; (f) and the other symptoms suggestive of gastric lesions are conspicuously absent.

Each of the patients here reported lived to over fifty years of age, and each had been a victim of recurrent gastric hemorrhage since early life. One of these patients in addition to giving a definite history of familial nasal, gastric and rectal bleeding, is also the father and the grandfather of victims of recurrent nosebleed. In Cases I and II, telangiectases detected on the gastric mucosæ were the sites of hemorrhage.

Case Reports. CASE I.—Male, aged thirty-two years, employed by the city fire department, was treated by me during a period of three years (ending in 1914), for recurrent attacks of gastric hemorrhage. Upon several occasions he passed considerable blood by rectum. Proctoscopic examination failed to reveal any evidence of hemorrhoids, or other pathology of the rectal mucosa. There were small telangiectases located on the face, scalp,

chest and lip. A tentative diagnosis of gastric ulcer, without pain or tenderness, was ventured. Hemorrhage from the stomach was first noted when a boy and while attending school. He was compelled to refrain from taking an active part in school athletics, because he occasionally vomited blood after strenuous exercise.

Family History. The patient's father had suffered from two severe attacks of gastric hemorrhage; and had also experienced the vomiting of a small amount of blood one or more times each year since a young man. The father was at this time sixty-four years of age and a sufferer from apoplexy; he vomited blood twice during the last year of his life, and died from cerebral hemorrhage.

Clinical Observation. Physical examination failed to detect anything abnormal except the small cutaneous telangiectases previously mentioned. The heart was normal; blood pressure, systolic 128, diastolic 80. The pulse was of good volume, regular and not influenced abnormally by exercise. Examination of the oral and nasal cavities gave negative findings.

While under my observation, he vomited blood seven times and reported rectal bleeding often. The quantity of blood ejected was never large, he ordinarily vomited from 2 to 4 ounces of blood-stained material. Chemical examination of this vomitus showed it to be acid in reaction, contained decomposed blood in certain instances, whereas two of the specimens showed many red blood cells and large clots. The attacks of vomiting blood were experienced twice after the too liberal imbibition in rich food and alcoholic beverages. During routine study, he was given an Ewald meal, the gastric content recovered and found to be normal. It was not possible at any time during this clinical observation, to elicit tenderness over the abdomen, and the patient contended that he never experienced discomfort either before, during or after the gastric hemorrhages.

Roentgen ray studies made at the Medico-chirurgical Hospital showed the stomach and intestine to be normal.

Laboratory Studies. The red blood cells were 3,710,000; leukocytes, 8,400 per c.mm.; hemoglobin, 76 per cent. A differential leukocyte count gave polymorphonuclears 68, small lymphocytes 23, large lymphocytes 5, eosinophiles 2, basophiles 1 and transitionals 1. Coagulation time (Boggs' coagulometer) was three minutes and fifteen seconds. The feces were examined upon several occasions for ova, and parasites with negative findings. Reaction of the feces for occult blood was positive.

While on duty, and attending a fire, he was compelled to work for several hours without his regular food or sleep. During this strenuous exertion he fainted and was brought to the hospital. Pursuant with a record of recurrent gastric hemorrhages and his present state of shock, I consulted with the late Professor Ernest LaPlace, who performed a laparotomy.

Findings. The visceral peritoneum appeared normal, except for a telangiectatic area, size of a pea, located upon the anterior surface of the gall bladder. The stomach contained a large volume of blood. Well toward the cardiac portion of the stomach, were two areas where the organ appeared to be unusually vascular. The stomach was opened in search of the bleeding site. The two hypervascular areas mentioned were pronounced by the surgeon to be small nevi, each being about one-fourth of an inch in their lesser diameter; and numerous bloodvessels were visible about these sections. Upon sponging these nevus-like areas, it was found that one of them bled after slight pressure, but to the naked eye, there was no actual erosion of either arteries or veins.

The operative procedure was the elective one of ligating an artery that supplied these highly vascular sections. The patient made a slow recovery and when last seen, five years after the operation, claimed he had not suffered an attack of gastric hemorrhage since operation.

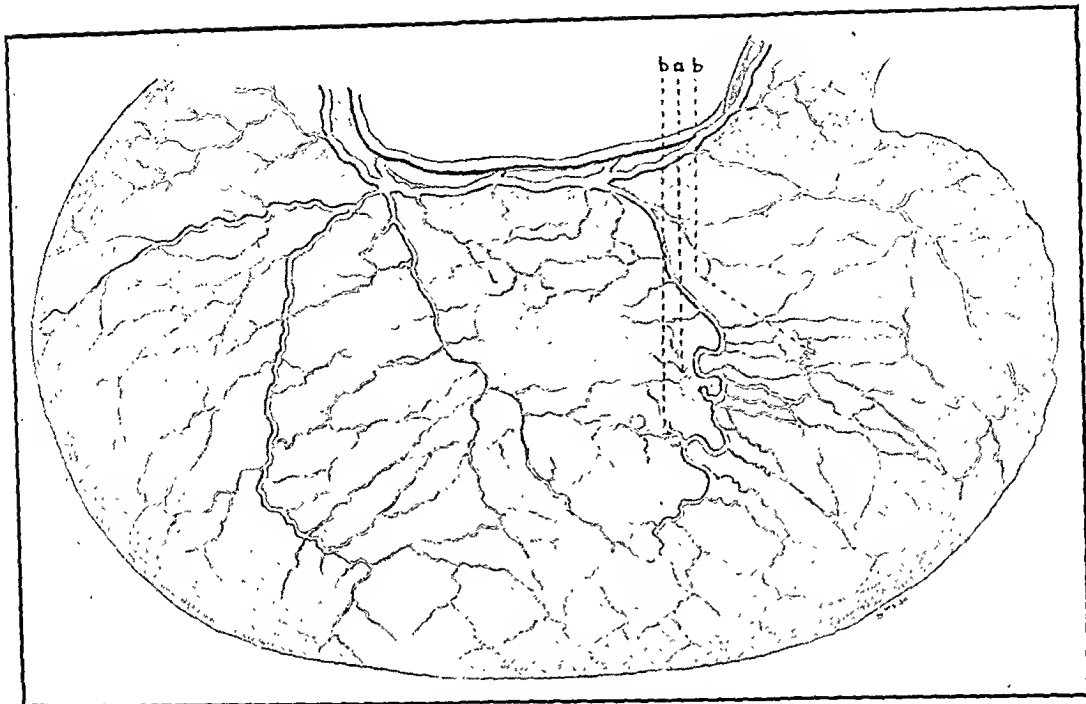


FIG. 1.—The stomach was opened along the greater curvature. Sketch shows venous distribution on the posterior wall. *a*, Lesion from which fatal hemorrhage occurred. *b, b*, two sections of the mucosa, showing extreme venous vascularity (these resembled telangiectases surrounded by minute plexuses of vessels). It was impossible to distinguish between small arteries and veins at these potential sites of bleeding.

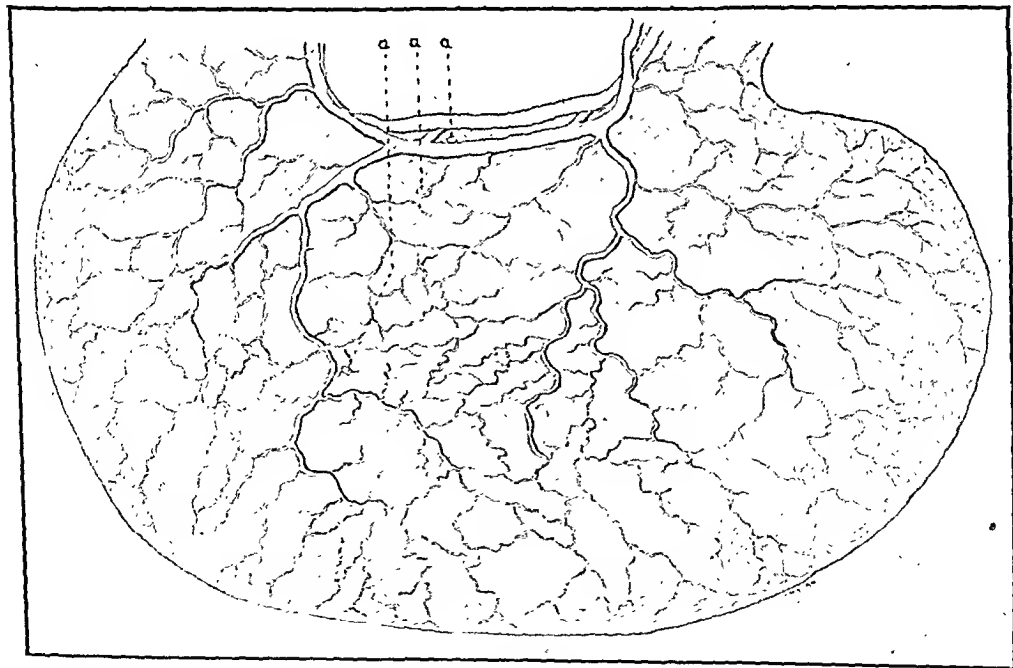


FIG. 2.—Sketch of venous supply of anterior wall of stomach (viewed from the peritoneal surface), while stomach was held in front of a strong light. *a, a, a*, Healed sites of previous hemorrhage. No sensation of thickening was detected, and they did not resemble the usual healed ulcer.

CASE II.—E. D., female, aged seventy years, admitted to the Woman's College Hospital, October 30, 1929, after vomiting 8 ounces of blood-stained fluid. She had had "stomach trouble" for years; recurrent attacks of faintness, usually mild but often severe enough to necessitate her sitting from one-half to several hours. Nausea was present, but vomiting rarely occurred. She had noticed recurrent attacks of bleeding from the rectum since early girlhood. The loss of blood through rectal hemorrhages did not impair her health. Four children are living, labors were normal.

Family History. Her mother died at seventy years, but was never a victim of attacks of hemorrhage. A maternal aunt suffered from recurrent attacks of nasal hemorrhage. A sister of the patient died at the age of fifty-six from repeated painless gastric hemorrhages. A brother died of apoplexy; three brothers living.

Present Illness. The patient enjoyed health until March, 1928, when, in the absence of other symptoms, she vomited about 2 quarts of blood-stained liquid. She was confined to the hospital for twenty-six days. She made an uneventful recovery, gained steadily in strength and weight. The hemoglobin rose from 30 to 70 per cent. Symptoms referable to stomach trouble were absent until October 30, 1929, when she entered the Woman's College Hospital. Slight chills and fullness in the stomach antedated vomiting, but pain was absent.

Physical Examination. A well-developed, white woman, weak and pale. A soft systolic murmur was heard at the apex and transmitted to the left axilla. Cardiac sounds were regular, but the muscle tone was poor. Gurgling sounds were active over the abdomen. A large scar covered the superior portion of abdomen, back and both arms, due to a burn by gas forty years ago. Two hours after admission (9 P.M.) the patient vomited 15 ounces of bright blood, and a half hour later, she again vomited 2 ounces of blood. Hemostatic serum (2 cc.) was given every two hours for 3 doses.

There was one small angiomaticous patch, 0.5 mm. in diameter on right eyelid at junction of the skin and mucous membrane. There were eight other telangiectases located on the neck, chest, abdomen, and right thigh. On the outer surface of right thigh near its center there were several areas of dilated bloodvessels about $1\frac{1}{2}$ inches in width and $2\frac{1}{4}$ to 3 inches in length, the longer measurements being nearly parallel with the femur. Inside of the right thigh were a few dilated vessels of the skin, and several telangiectases on the left leg.

The urine was amber in color, acid, specific gravity 1020, and contained a trace of albumin; otherwise negative.

On account of extensive scarring from previous burns, a successful transfusion was impossible. On admission the blood examination revealed hemoglobin, 60 per cent; erythrocytes, 3,370,000; leukocytes, 6,700; clotting time, three and a half minutes. Subsequent blood examinations revealed a rapid decrease in both erythrocytes and hemoglobin. Blood platelets numbered 340,000.

Four days after admission the patient suddenly became nauseated and vomited 4 ounces of blood, followed by sweating, chills, weak rapid pulse and restlessness. She died on the fifth day following severe gastric hemorrhage.

Pertinent Autopsy Findings. The esophagus was normal. The stomach contained 1 pint of blood and a large clot. On the posterior surface, 5 cm. from the esophageal opening, was an erosion 0.5 cm. in diameter, the center of which was occupied by a vessel whose mouth was plugged by a clot. By holding the stomach against the light it was seen that this vein communicated with a large branch of the coronary veins (Fig. 1). Toward the lesser curvature (on the anterior wall) were three minute white scars smaller than a pin's head (Fig. 2). These scars were situated along the course of

the veins. Each scar was located on a portion of highly vascular mucosa. When held up to the light, a minute yellow-white thickening could be seen surrounded by a thin white halo. None of the scars, or the lesion at site of hemorrhage felt thickened at autopsy, but after hardening the organ, it was possible to feel slight thickening of these scars with the ungloved hand. The intestines were filled with thick, tarry blood. The upper part of the small intestine was discolored red, the lower part reddish black and the colon black from the presence of blood.

CASE III.—Male, age sixty years, first seen by me in 1925.

Chief Complaint. Obstinate constipation, recurrent attacks of tenderness over the upper abdomen, followed by nausea and faintness. Gastric distress at times became severe and the pain was only relieved by the taking of food. He had repeatedly vomited during these attacks and the vomitus usually contained some blood. It was his custom to pass a small amount of blood from the bowel the day following these seizures.

Family History. The mother, a maternal grandfather and a maternal uncle and the patient's sister had suffered from recurrent attacks of nose-bleed. The patient has a son and a grandson who are also sufferers from familial telangiectasis, both of whom experienced their first attack of nasal hemorrhage at about the tenth year of age. The inherent tendency to transmit the pernicious defect of telangiectasis is well exemplified by this patient.

Physical Examination. Physical examination revealed nothing of clinical importance except the presence of small telangiectases situated on the neck, trunk and nasal mucosa. He had received treatment (cauterization) for "spider nevi" located on the nasal mucosa.

Conclusion. Familial telangiectasis is the etiologic factor in a definite class of hemorrhage, which takes place in the presence of normal physiologic responses by both the capillary and venous blood. Recurrent gastric hemorrhages were experienced during early life by each of the 3 cases studied; and attacks of hemorrhage were often accompanied by brief periods of syncope. Judging from the small number of case reports available, familial telangiectasis does not shorten the span of life or inhibit development. Familial gastric hemorrhage has been observed, in persons who have also experienced recurrent attacks of hemorrhage from other mucous surfaces. The vascular defects common to familial hemorrhages from the mucous membranes are to be found among other members of the same family and in their near relatives. The tendency to familial hemorrhage is transmitted by both maternal and paternal parent to offspring.

REFERENCES.

1. Wilson: J. Cutan. Med. and Dis. Skin, 1869, 3, 198.
2. Fox. Brit. J. Dermat., 1908, 20, 145.
3. Phillips: Proc. Roy. Soc., London, 1908, 1, 64.
4. Hutchinson and Oliver: Quart. J. Med., 1916, 9, 67.
5. Pringle: Proc. Roy. Soc. Med., London, 1912, 6, 129.
6. Boston: Med. Times, 1930, 58, 68.

THE EFFECT OF LIVER EXTRACT ON THE BLOOD OF NORMAL PERSONS.*

BY MARTIN P. CRANE, M.D., ISABEL HOWARD,

AND

WILLIAM P. MURPHY, M.D.,

INSTRUCTOR IN MEDICINE, HARVARD MEDICAL SCHOOL; ASSOCIATE IN MEDICINE,
PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.)

THAT the ingestion of liver extract may cause in a normal person a prompt and striking rise in the red blood cell count accompanied by symptoms and signs of polycythemia is a fascinating problem for speculation. Watkins, Johnson and Berglund¹ observed a rise in the red blood cell count to as high as 7,800,000 and the simultaneous occurrence of symptoms of headache, epistaxis, vertigo and with particularly acrocyanosis. They suggest that the action of the unknown substance or substances contained in the extract which are effective in allowing an increase of red blood cells in pernicious anemia act in the manner of a stimulant for the maturation and discharge of normal red blood cells. Inasmuch as these observations have not been corroborated up to the present time, the following studies were made.

Procedure. Following control studies, during which the normal blood values were determined, the contents of eight vials of a potent liver extract,† the equivalent of 800 gm. of liver, were ingested daily for a period of fourteen days by four normal young men. During the period of observation each took his customary normal diet.

In the observation period red blood cell counts were made from blood obtained from an ear-lobe puncture, twice daily, at approximately 10 A.M. and 3 P.M. Counts were made from two United States Bureau of Standards standardized pipettes each time and the average of the two counts recorded. The reticulocytes were counted in smears of the blood made at the same time and stained with brilliant cresyl blue.

Before treatment was begun, and at weekly intervals thereafter, observations were made on venous blood as follows: The percentage of blood hemoglobin (Sahli), red blood cell count, the total cell volume by hematocrit, individual cell volume,² blood iron,³ icteric index⁴ and the mean red blood cell diameter by measurements.

Observations. The reticulocyte response was as follows: On the fifth day in each subject there occurred a distinct increase from

* This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic disease.

† Supplied by Eli Lilly & Co.

control values reaching 3, 1.3, 1.4 and 1.1 per cent respectively. Although the percentage increase is small, it is to be noted that on the basis of 5,000,000 circulating red blood cells per cubic millimeter, this would give actual reticulocyte figures of between 150,000 and 55,000 per c.mm. These figures would compare with a 15 per cent reticulocyte rise in a patient with 1,000,000 red cells per c.mm., as in severe pernicious anemia. The rise was transitory, persisting for from one to three days, following which the values decreased apparently to below the control figures.

TABLE I.

Time.	Red blood cells per c.mm.	Hemoglobin (cap.).	Hemoglobin (ven.).	Reticulocytes, per cent.	Hematocrit, per cent of cells.	Individual cell volume	Blood iron.	Mean diameter, microns.
A.M.	5,050,000(V)	..	113	0.7	46.5	9.2	46.14	7.62
P.M.	4,440,000	118	..	0.6				
A.M.	4,890,000	113	..	0.6				
P.M.	5,010,000	114	..	0.5				
A.M.	5,040,000	113	..	0.4				
A.M.	...	Liver extract started.						
A.M.	5,060,000	119	..	0.4				
P.M.	5,200,000	115	..	0.6				
A.M.	5,050,000	116	..	0.7				
P.M.	5,010,000	114	..	0.8				
A.M.	5,080,000	116	..	0.5				
P.M.	4,980,000	114	..	0.6				
A.M.	5,200,000	114	..	0.6				
A.M.	5,110,000	114	..	3.0				
P.M.	5,180,000	115	..	1.2				
A.M.	5,260,000	116	..	1.5				
P.M.	5,200,000	115	..	0.7				
A.M.	5,290,000	116	..	1.0				
P.M.	5,110,000	116	..	0.6				
A.M.	5,010,000	118	..	0.4				
	4,960,000(V)	..	119	..	46.5	9.3	54.30	7.63
P.M.	5,030,000	114	..	0.3				
A.M.	5,020,000	116	..					
P.M.	5,110,000	116	..	0.3				
A.M.	5,380,000	116	..	0.2				
P.M.	5,210,000	115	..	0.3				
A.M.	5,280,000	116	..	0.2				
A.M.	5,400,000	118	..	0.3				
A.M.	5,330,000	118	..	0.3				
A.M.	5,290,000(V)	..	118	..	45.9	8.6	49.80	7.67
	5,500,000	120	..	0.4				

V = Venous blood used.

An analysis of the red blood cell counts revealed them in similar fashion to have been moderately affected. The greatest increase occurring, as shown in Table I, did not exceed 700,000 from the average control value, while in Tables II and III the greatest increase was not in excess of 300,000 from the average of their respective control values.

TABLE II.

Time.	Red blood cells per c.mm.	Hemoglobin (cap.).	Hemoglobin (ven.).	Reticulocytes, per cent.	Hematocrit, per cent of cells.	Individual cell volume	Blood iron.	Mean diameter, microns.
A.M.	5,090,000(V) 4,980,000	.. 112	114 0.7	40.6	7.9	42.02	7.69
A.M.	4,090,000	109	..	0.5				
A.M.	5,110,000	107	..	0.4				
Liver extract started.								
A.M.	5,140,000	109	..	0.5				
P.M.	5,080,000	104	..	0.5				
A.M.	5,170,000	107	..	0.5				
P.M.	5,020,000	109	..	0.6				
A.M.	5,020,000	107	..	0.4				
P.M.	5,030,000	108	..	0.4				
A.M.	5,080,000	106	..	0.5				
A.M.	5,130,000	106	..	0.7				
P.M.	5,240,000	108	..	1.3				
A.M.	5,340,000	110	..	0.9				
P.M.	5,460,000	108	..	0.8				
A.M.	3,300,000	110	..	0.5				
P.M.	5,100,000	110	..	0.4				
A.M.	4,940,000	110	..	0.3				
	5,020,000(V)	..	117	..	47.3	9.4	45.30	8.05
P.M.	4,990,000	108	..	0.3				
A.M.	5,180,000	110	..	0.3				
A.M.	5,480,000	110	..	0.3				
P.M.	5,190,000	111	..	0.3				
A.M.	5,230,000	112	..	0.2				
A.M.	5,400,000	112	..	0.3				
A.M.	5,480,000	113	..	0.3				
	5,220,000(V)	..	112	..	45.9	8.8	46.80	7.63
	5,630,000	113	..	0.3				

V = Venous blood used.

In Table IV the onset of an acute upper respiratory infection in this subject on the eighth day forced him to discontinue the extract. However, up to that time the findings in his case were in accord with the others. The counts on the whole show a tendency toward a moderate but sustained red blood cell elevation during the latter

half of the experiment. There was, however, no evidence of an immediate or excessive rise to striking values in any case.

TABLE III.

Time.	Red blood cells per c.mm.	Hemoglobin (cap.).	Hemoglobin (ven.).	Reticulocytes, per cent.	Hematocrit, per cent of cells.	Individual cell volume	Blood iron.	Mean diameter, microns.
A.M. . .	5,000,000(V)	..	107	..	43.8	8.7	42.84	7.73
	5,010,000	109	..	0.5				
A.M. . .	5,140,000	108	..	0.7				
P.M. . .	5,080,000	109	..	0.5				
A.M. . .	5,110,000	110	..	0.4				
Liver extract started.								
A.M. . .	5,060,000	111	..	0.3				
P.M. . .	5,030,000	120	..	0.5				
A.M. . .	5,200,000	107	..	0.6				
P.M. . .	5,070,000	116	..	0.5				
A.M. . .	5,180,000	117	..	0.4				
P.M. . .	5,050,000	109	..	0.4				
A.M. . .	5,200,000	114	..	0.5				
A.M. . .	5,180,000	110	..	1.1				
P.M. . .	5,320,000	109	..	1.4				
A.M. . .	5,540,000	112	..	1.0				
P.M. . .	5,380,000	111	0.8					
A.M. . .	5,340,000	110	..	0.6				
P.M. . .	5,020,000	112	..	0.4				
A.M. . .	5,040,000	110	..	0.4				
	4,980,000(V)	..	109	..	45.3	9.0	46.8	7.91
P.M. . .	5,090,000	111	..	0.3				
A.M. . .	5,100,000	112	..	0.3				
P.M. . .	5,190,000	112	..	0.3				
A.M. . .	5,510,000	112	..	0.3				
P.M. . .	5,210,000	110	..	0.2				
A.M. . .	5,260,000	112	..	0.3				
A.M. . .	5,320,000	114	..	0.3				
A.M. . .	5,340,000	114	..	0.4				
A.M. . .	4,990,000(V)	..	115	..	43.8	8.8	46.8	7.65
	5,390,000	114	..	0.3				

V = Venous blood used.

Hemoglobin values were not greatly altered, but point again toward a higher general average in the latter days of the test.

The blood-iron level was slightly increased in 3 subjects. The individual cell volumes showed a slight intermediate increase, due perhaps to the increased number of young cells, although the

diameters were irregularly affected, giving an intermediate rise in 2 cases with a later return to control sizes.

TABLE IV.

Time.	Red blood cells per c.mm.	Hemoglobin (cap.).	Hemoglobin (ven.).	Reticulocytes, per cent.	Hematocrit, per cent of cells.	Individual cell volume	Blood iron.	Mean diameter, microns.
A.M. . .	4,600,000(V)	..	98	..	39.5	8.4	40.50	7.61
A.M. . .	4,610,000	100	..	0.6				
A.M. . .	4,890,000	105	..	0.5				
A.M. . .	4,990,000	104	..	0.5				
A.M. . .	5,180,000	105	..	0.5				
Liver extract started.								
A.M. . .	5,102,000	103	..	0.4				
P.M. . .	5,010,000	105	..	0.7				
A.M. . .	5,120,000	104	..	0.4				
P.M. . .	4,990,000	105	..	0.5				
A.M. . .	5,100,000	104	..	0.4				
P.M. . .	5,140,000	104	..	0.7				
A.M. . .	5,160,000	104	..	0.8				
A.M. . .	4,990,000	105	..	1.1				
P.M. . .	5,090,000	105	..	0.7				
A.M. . .	5,060,000	105	..	0.5				
P.M. . .	5,100,000	104	..	0.5				
A.M. . .	4,890,000(V)	..	102	..	41.0	8.5	41.50	7.96
	5,090,000	104						

V = Venous blood used.

The icteric index remained normal throughout.

The only subjective symptoms noted during the course of the experiment were a moderate nausea which followed almost immediately after taking a fairly large dose (3 or 4 vials) upon an empty stomach and a slight diarrhea lasting from four to six days. No headache, dizziness, epistaxis or acrocyanosis occurred. The subjects in general felt quite well.

These findings are very much in accord with certain other investigations. Minot, Murphy and Stetson,⁵ using cooked liver, were able to demonstrate only trivial increase in either hemoglobin or red blood cells. Similarly, Neidhardt and Bannasch,⁶ on diets of 500 gm. of raw liver for periods up to thirty days, obtained only slight increases in red blood cells and hemoglobin. Jungmann,⁷ with a diet identical with that of Neidhardt and Bannasch, reported that the red blood cell counts were practically unchanged. Cornell⁸

found no change in the blood of 4 normal persons who ingested 240 gm. of raw liver pulp daily for four weeks.

From these observations one may conclude that blood formation in normal individuals may be enhanced by the ingestion of large amounts of liver or liver extract, but that a striking change does not occur.

Neidhardt and Bannasch believe that there is an increased hemolysis, as shown by the increase of urobilin in the urine; but on the one hand the urobilin determination in the urine is a very crude one, and a quantitative determination of urobilin in both stool and urine would be necessary to demonstrate an increased hemolysis. On the other hand, the icteric index in our cases was not increased, which indicates that no pathologic hemolysis took place. The urine tested for urobilin at the conclusion of our observations was negative.

As suggested by Minot and Murphy,⁹ and later substantiated by the work of Castle,¹⁰ it is very probable that liver contains an essential element which is necessary for the formation of normal and durable red blood cells. Only if this factor is absent, and the red blood cell count low, as in pernicious anemia, do we get the typical and striking liver effect.

Conclusions. 1. There was observed a slight rise in the reticulocytes, an increase in red blood cells and percentage of hemoglobin, together with a slight rise in the blood-iron level following the ingestion of the contents of 8 vials of liver extract daily.

2. Striking changes in the blood did not occur nor were the clinical symptoms or signs of polycythemia observed during such treatment.

3. There was no evidence to suggest increased hemolysis of the blood during the period of observation.

BIBLIOGRAPHY.

1. Watkins, C. H., Johnson, R., and Berglund, H.: The Effect of Liver Extract on Erythrocytes and Reticulocytes in Normal Individuals, *Proc. Soc. Exp. Biol. and Med.*, 1928, 25, 720, 835.
2. Murphy, W. P., and Fitzhugh, G.: Red Blood Cell Size in Anemia; Its Value in Differential Diagnosis, *Arch. Int. Med.* (in press).
3. Murphy, W. P., Lynch, R., and Howard, I.: The Value of Whole Blood Iron Determinations (in press).
4. Murphy, W. P.: Biliary System Function Tests, *Arch. Int. Med.*, 1926, 37, 797.
5. Minot, G. R., Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy, *Am. J. Med. Sci.*, 1928, 175, 581.
6. Neidhardt, K., and Bannasch, K.: Effect of Liver Diet on Healthy Organism, *Ztschr. f. klin. Med.*, 1929, 111, 292.
7. Jungmann, P.: The Mechanism of Liver Treatment in Pernicious Anemia, *Klin. Wehnschr.*, 1928, 7, 441.
8. Cornell, B. S.: Effect of Liver in the Diet of Normal Persons, *Canadian Med. Assn. J.*, 1928, 28, 394.
9. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia, *J. Am. Med. Assn.*, 1927, 89, 759.
10. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Am. J. Med. Sci.*, 1929, 178, 748, 764.

THE INFLUENCE OF GASTRIC JUICE ON ERYTHROPOIESIS IN PERNICIOUS ANEMIA.

BY WILLIAM S. MIDDLETON, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE.

AND

R. H. STIEHM, M.D.,

SENIOR RESIDENT IN MEDICINE, MADISON, WIS.

(From the Department of Medicine, University of Wisconsin.)

A COMPREHENSIVE survey of the data suggesting a causal relationship between the gastrointestinal tract and pernicious anemia, in 1926, by Ivy,¹ constitutes an accurate résumé of the literature to that date. For the present purposes suffice it to say that for years laboratory and clinical evidence had been accumulating in support of this interrelation. On one point only had there developed an unanimity of opinion among workers in this field, namely, the constancy of achylia gastrica in patients with pernicious anemia. Levine and Ladd² in an analysis of 143 cases of pernicious anemia reported the astounding figure of 99 per cent in which achlorhydria was established. All of the further evidence in this matter was, as the above, purely inductive for a causal relationship between the two conditions, and it is beyond the scope of the present note to reiterate these details.

It remained for Castle^{3,4,5,6} in a series of original and revealing studies to attack this problem by the direct method of experimentation. His observations may be listed as follows:

(a) The product of the normal gastric digestion of a beef meal, regurgitated and then further incubated *in vitro* with hydrochloric acid, when fed to patients with pernicious anemia, induced reticulocyte responses with remissions in the blood picture comparable to those from liver therapy.

(b) Beef alone is incapable of such action.

(c) Diluted hydrochloric acid will not induce such reactions.

(d) The product of the interaction between beef on one hand and commercial pepsin and hydrochloric acid on the other, *in vitro*, proved inert.

(e) Normal gastric juice and beef incubated together *in vitro* with hydrochloric acid and then administered to patients with pernicious anemia gave rise to characteristic remissions.

(f) Normal gastric juice incubated *in vitro* with an indifferent protein as casein developed no potency with reference to erythropoiesis.

(g) Normal gastric juice administered alone and at a sufficient interval after meals led to no regular erythropoietic response. Where

a slight response was noted, still further rises resulted when similar quantities of gastric juice and beef muscle were incubated together *in vitro* and then given to the same subjects.

Wilkinson⁷ reported results rather contradictory to those of Castle on the administration of gastric juice to a patient with pernicious anemia. Exercising due precautions to obtain an active normal gastric juice with or without histamin, 150 to 200 cc. was given during meals. (It is not possible to determine from the report whether this amount represents the total dosage for a day or that given at each of three meals.) The single case cited in detail received 150 to 200 cc. of fresh gastric juice daily with the noonday meal. The initial level of erythrocytes was 3,850,000 and the hemoglobin 100 per cent. A control period of exhibition of hydrochloric acid and pepsin had led to a decline in the blood picture. On the administration of gastric juice a reticulocyte rise to 4 per cent was noted on the twenty-fourth day, when the erythrocytes numbered over 4,000,000. It will be noted that the initial level of erythrocytes (3,850,000) precluded a true reticulocyte response⁸ regardless of the agent used. While the reticulocyte rise is appreciable considering this point, the author is not justified in attributing the subsequent fall of the reticulocytes to the institution of liver therapy. Reticulocyte responses in pernicious anemia to any form of therapy are not to be anticipated with erythrocyte counts exceeding 3,000,000.

In view of the possible question awakened by Wilkinson's report and the difficulties attendant upon clinical studies of this type the two following experiences are cited:

Case Reports. CASE I.—A white, single male, farmhand, aged forty-one years, was admitted to the Hospital on November 7, 1929, with a history of weakness, which began the previous January with an attack of so-called "flu," at which time he was delirious. Convalescence was marked by weakness and pallor, and in February he was told to take 1 vial of liver extract daily. This dosage was continued up to the time of admission, except for a period of three weeks in June. He consulted a physician in July when the weakness became more marked and was advised that liver therapy be continued and that iron be added. Weakness, however, continued unabated and in October, 1929, the patient was forced to go to bed, where he remained until admission to the hospital. His history also included recurrent soreness of the tongue, epistaxis, dyspnea, nocturia, and 27 pounds loss of weight since January, 1929. Past medical, social, and family histories were irrelevant.

The pertinent physical findings included a sallow, lemon-colored skin, oral sepsis, dental caries, atrophic tongue with visible papillæ, pale mucous membranes, venous hum at the base of the neck, systolic murmur over entire precordium, palpable liver edge, quadriceps and general muscular weakness, and decreased vibratory perception over the tibiæ.

Laboratory examination on admission showed an erythrocyte count of 1,050,000, with a hemoglobin of 20 per cent. Fractional aspiration of the gastric contents following subcutaneous histamin injection revealed the absence of free hydrochloric acid. The stools contained no ova, parasites nor motile organisms. The icterus index was 15.

A diagnosis of pernicious anemia with early cord involvement was made, and the failure of response to a potent liver extract was attributed to the inadequate dosage.

The day following admission 100 cc. of gastric juice was given with each meal. The average titration of this gastric juice showed a free acid content of 33 degrees. This procedure was continued for a period of six days without a reticulocyte response. The erythrocyte count at the conclusion of this period showed 630,000 cells, with less than 10 per cent hemoglobin. Because of the patient's precarious condition liver extract (Eli Lilly & Co. No. 343), 1 vial three times a day was begun; and in the absence of an adequate response in the blood picture at the end of a further period of six days, a blood transfusion was given. Following this procedure a further reticulocyte response was noted with a rise in the erythrocyte counts. Twelve days after the blood transfusion and after eighteen days of administration of liver extract (equivalent of from 300 to 500 gm. of liver daily) the erythrocyte count was 3,270,000, with 53 per cent hemoglobin. Hence the response of the blood picture to accepted therapy would be deemed satisfactory (Fig. 1).

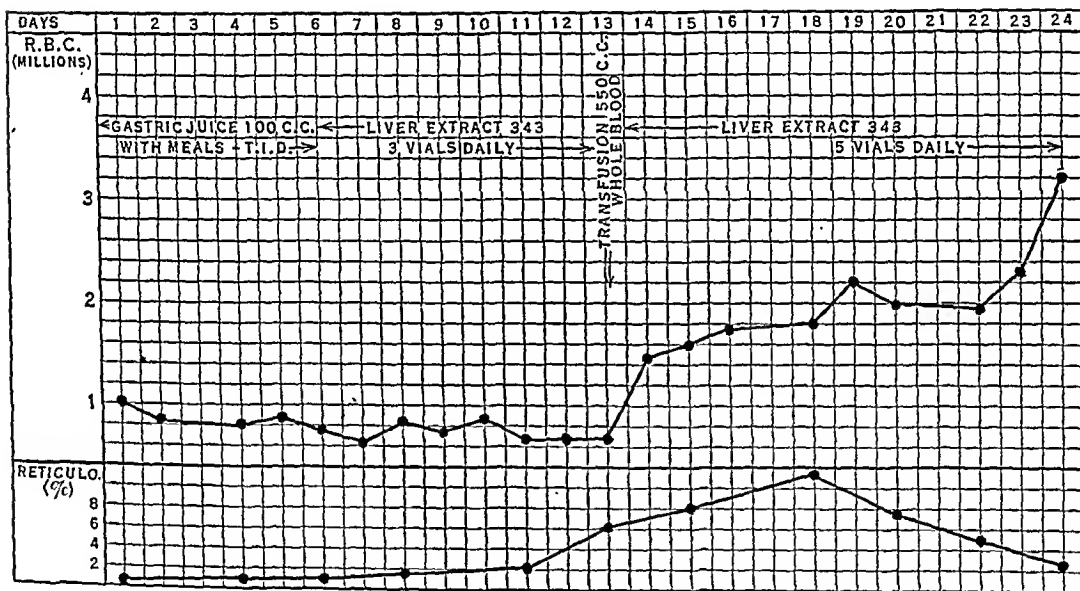


Fig. 1

CASE II.—A retired white farmer, aged seventy-three years, was readmitted to the Hospital on December 9, 1929, having been discharged on December 12, 1928 with a diagnosis of pernicious anemia after an excellent remission from liver therapy. Shortly after his discharge he had neglected to continue with the liver extract as advised; and on readmission physical examination again showed the lemon-yellow pallor, bald tongue, cardiac enlargement, palpable liver and right kidney, thickening of the radial arteries, loss of vibratory sensation in the lower extremities, and general muscular weakness of his earlier hospital stay.

Laboratory examinations on admission included a blood count of 1,640,000 erythrocytes, with 35 per cent hemoglobin. The icterus index was 8.

A diagnosis of pernicious anemia with posterolateral degeneration of the cord was reaffirmed.

Beginning the day following admission, the patient was given 200 cc. of

gastric juice with each meal. The average titration showed a free acid content of 33 degrees. Nine days after this treatment was begun, the average reticulocyte count was somewhat above normal, but their number never exceeded 5.2 per cent of the total erythrocytes. At the end of eighteen days, the patient was discharged. His blood count then showed 1,550,000 red blood cells and 47 per cent hemoglobin (Fig. 2).

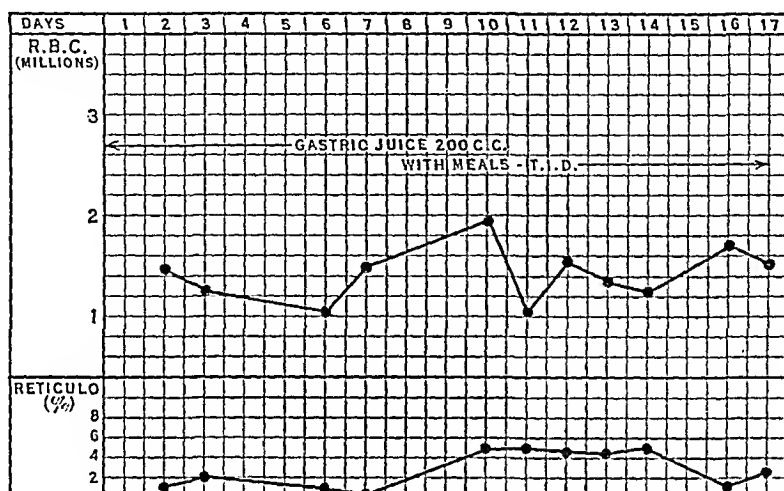


FIG. 2

Discussion. Before entering upon a discussion of these cases certain details of procedure must be considered. In the first place the gastric juice utilized in this study was the pooled product of a number of gastric aspirations. Histamin was not utilized to augment the gastric secretion in any instance. The normal gastric juice obtained was titrated for free acidity, and if found to be within normal range, the same was passed through a Berkefeld filter, sealed in sterile flasks and kept in an icebox. Daily determinations for acidity and sterility were made, and interestingly the gastric juice maintained its free acidity with little or no fluctuation for as long as six weeks. At the same time sterility was preserved. This observation, of course, placed the responsibility for the usual loss of free acidity when a gastric content is allowed to stand upon bacterial or fungous growth and proteids, such as mucin, which may be removed by the Berkefeld filter.

In analyzing the results of the administration of normal gastric juice to these 2 patients, one notable difference presents itself, namely, a low-grade response of the reticulocytes in Case II as compared with an absence of response in Case I. In neither instance did a significant numerical rise of the erythrocytes occur. It may be argued that Case I did not receive the gastric juice in sufficient quantity (one-half the daily amount received by Case II) nor long enough to manifest a hematopoietic effect, whereas Case II obviously had an adequate trial. This argument cannot be controverted. In view of Castle's observations,⁶ what would seem a more logical

explanation of the difference resides in the fact that while both received the same diet, Case II ate his meat regularly and Case I was unable to partake of the same. As Castle⁶ has pointed out, the interaction between ingested beef and normal gastric juice administered close to the former may readily occur in the stomach of a pernicious anemia patient with a resultant product which is responsible for the blood remissions in pernicious anemia.

Conclusion. In conclusion it may be stated that these studies, meager though they be, support Castle's contention that normal gastric juice alone does not contain the active maturing factor essential to erythropoiesis.

REFERENCES.

1. Ivy, A. C.: The Relation of the Gastrointestinal Tract to Pernicious Anemia, *Northwest Med.*, 1926, 25, 399.
2. Levine, S. A., and Ladd, W. S.: Pernicious Anemia: A Clinical Study of 150 Consecutive Cases with Special Reference to Gastric Anacidity, *Bull. Johns Hopkins Hosp.*, 1921, 32, 254.
3. Castle, W. B., and Locke, E. A.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *J. Clin. Invest.*, 1929, 6, 2.
4. Castle, W. B.: The Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Proc. Roy. Soc. Med.*, 1929, 22, 58.
5. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients With Pernicious Anemia of the Contents of the Human Stomach Recovered After the Ingestion of Beef Muscle, *AM. J. MED. SCI.*, 1929, 178, 748.
6. Castle, W. B., and Townsend, W. C.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, *AM. J. MED. SCI.*, 1929, 178, 764.
7. Wilkinson, J. F.: Pernicious Anemia—Preliminary Report on the Results Obtained by Treatment with Certain Preparations of Stomach, *British Med. J.*, 1930, i, 236.
8. Minot, G. R., Murphy, W. P., and Stetson, R. P.: Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia, *AM. J. MED. SCI.*, 1928, 175, 581.

INCIDENCE OF THE SICKLE-CELL TRAIT IN INDUSTRIAL WORKERS.

BY G. M. BRANDAU, B.A., M.D.,

HOUSTON, TEXAS.

THE attention of the profession has been drawn repeatedly during the past two decades to the occurrence of a new or newly-discovered nosologic entity which, on account of a numerical decrease of the red blood corpuscles, associated with a peculiar crescentic conformation of a varying percentage of these cells, has been designated sickle-cell anemia. The occurrence of such cells was first noted in 1889 by the French hematologist, Hayem,¹ and in 1910 Herrick,² of Chicago, reported a case of sickle-cell anemia, thus giving an impetus to the study of the disease in this country.

The most characteristic signs and symptoms of this disease appear to be a yellow or greenish-yellow discoloration of the scleræ, presence or history of leg ulcer, abdominal crises, lymph glandular enlargement, muscle and joint pains, sickle cells varying from 1 to 95 per cent of the total number of red blood corpuscles, anemia and urobilinuria. During the acute phases of the disease there is moderate pyrexia. The spleen may or may not be enlarged. The condition occurs almost exclusively in the negro race, although 1 case has been reported in an Arab boy, who possibly had some admixture of negro blood,³ and 4 white cases^{4,5} have been described in which there was no evidence to sustain any suspicion of an Ethiopian taint. It is marked by remissions and exacerbations, the remissions being largely devoid of subjective symptoms, and accompanied by improvement in the objective signs, as well as a corresponding change in the laboratory findings. Aside from the disease itself, and in a large majority of cases occurring without active signs of ill health, the phenomenon of drepanocytosis is observed in the sickle-cell state, trait or aptitude or latent sickle-cell anemia, as it is variously called. The term latent sickle-cell anemia should not, however, be used as a synonym of sickle-cell trait, but if employed at all, should be reserved to designate those periods of remission in drepanocytic anemia when the disease is practically quiescent. It seems to be established that the anemia occurs more frequently in those with the sickle-cell trait than in those whose blood is normal in this respect; in other words, that the trait is a predisposing factor in the development of the anemia.⁹ Some authors even regard the trait as a very mild form of the disease, of which the active anemia is a severer manifestation,⁶ although the former has been found to be entirely compatible with good health and with long life, while the latter is not considered conducive to either. The trait has been observed to remain in some cases after the anemia and its accompanying symptoms have cleared up⁴ (remissions) and even after splenectomy^{8,9,10} (presumptive cure). The distorted cells or poikilocytes found in these conditions are designated drepanocytes, from the Greek word, *δρεπάνος*, meaning sickle, and the name is thus descriptive of the morphology. They have also been called meniscocytes in reference to their crescentic shape. The drepanocytic status has been reported from different cities as occurring in from 5¹¹ to 7⁹ or 7.5¹² per cent of the negroes examined. These figures represent the incidence in hospital or dispensary patients who presumably were present because of disease or injury. In order to determine the incidence among the negro male population in this locality it was decided that 100 negro applicants for employment should be examined, though to date nearly twice that number have been subjected to study. Interest was felt also in the question of the ratio of the occurrence of the sickle-cell trait in patients applying for treatment to that in healthy workers applying for remunerative occupation. The investigation was under-



Sickle cells in moist preparation. Variations in shape in the distorted forms are evident. In the smaller cells the refractive index appears to be increased.

taken primarily to ascertain whether or not the sickle-cell trait is to be regarded as a definite industrial hazard. The examination in each instance consisted of three parts:

1. A brief history inquiring into past illnesses, with special reference to the occurrence of joint and muscle pains, abdominal crises and ulcers.

2. A general physical examination, giving particular attention to scleral color anomalies, lymph-node enlargement and hypertrophied tonsils, ulcers, especially *ulcus cruris* or resultant scars, and condition of the abdomen.

3. Study of moist blood films made by placing a drop of fresh blood on a slide, covering it with a coverslip and sealing with vaseline to prevent drying. These preparations were then observed daily for six days or longer.

As the individuals examined were all applying for work, some of them were no doubt unduly reticent in relating their previous untoward symptoms, and to that extent the histories must be discounted. The number who had "never been sick a day in their lives" was almost unbelievably large. Nevertheless, with the use of patience and diplomacy, it is believed fairly accurate data were secured. Yet in only 1 of those with positive blood findings did the history disclose any symptoms in the past which might possibly have been interpreted as representing the acute phase of the disorder or active drepanocytic anemia. In this case there was a history of an acute attack of "rheumatism" at twenty-two years of age (the present age being forty-two years) and of attacks of "indigestion" following dietary indiscretions, these attacks being of infrequent occurrence and distributed over a long period of time. In those with negative blood findings there was a history of joint pains in 3, of indigestion or abdominal cramping in 15 and of leg ulcers in 2. The small number of positives used in the comparison, and the manifold interpretations which might be accorded the symptoms mentioned, would rob these figures of any significance except to indicate that the history is of but little value in detecting individuals possessed of the sickle-cell trait. Certain symptoms as related in the anamnesis might, however, be regarded as suggestive of the condition, although a negative history would not necessarily nullify a presumption of its presence. As the sickle-cell trait has been demonstrated in patients who have had sickle-cell anemia,⁴ a clear history of this disease would at least be suggestive of the presence of the trait.

The physical examinations not only did not reveal any pathognomonic sign associated with the sickle-cell condition, but also failed to demonstrate any probable sign or syndrome on which a diagnosis might reasonably be hazarded. In only 5 of the 100 subjects were the scleræ and episcleræ clear and devoid of some color changes, although none of these 5 were in the positive group. The predominating color was a brownish hue, sometimes with flecks of a darker

brown tint; occasional variations were yellowish-brown, cream colored or even reddish-brown. Quite a few (16) showed a light slaty-blue tint of the scleræ, with perhaps 2 or 3 dark-blue pin-head-sized macules on this background. However, none of these latter were found to have sickle cells, nor was there any indication that these blue sclerotics were of the type associated with fragility of the bones.

The inguinal lymph nodes were palpable in 95 per cent of the men examined and in all of the positive cases. General lymphadenopathy was noted in 2 of the positive and in 30 of the negative cases, thus maintaining practically the same proportion. In none of the positive cases was the spleen demonstrably enlarged. Leg ulcers were not present in any of the men examined. The age, weight, blood pressure, muscular tone and development, presence of focal infections and bluish mottling of gums and palate were likewise considered and found to be apparently without bearing or influence on the condition. It occurred both in the pure black and in those of mixed blood. The typical greenish-yellow scleræ of the active anemia is dependent on erythrocyte destruction and, as was to be expected, was not observed with the sickle-cell state. The same remarks are applicable to the urobilinuria, Erlich's aldehyde test showing absence of that condition in the positive cases reexamined. Urobilinuria, however, has been reported in the sickle-cell trait, apparently in the absence of active hemolysis.

In examining the slides for sickle cells it was observed that the red corpuscles assumed the typical shapes after varying lengths of time, the phenomenon occurring sometimes on the first day and sometimes as late as the fifth day. The change is probably brought about in susceptible cells by the consumption of oxygen and the formation of carbon dioxide resulting from cell metabolism.⁹ Other factors are not without influence.^{9,4} Being unfamiliar with the study of moist preparations, some confusion was at first occasioned by the occurrence of poikilocytes not of the typical sickle-cell shapes. In these slides the red blood cells appeared smoothly outlined and distorted into various shapes, such as cup-shaped, club-shaped, horseshoe-shaped, sinuous forms, falcate, scaphoid and others. This change was found usually in drying films, and it is thought was due to osmosis through the cell membrane, though not all drying films showed this change. Reexamination of the men in this group gave negative results, and similar forms were noted in a control series in Mexicans; hence, the slides were not regarded as positive. Some difficulty was experienced in attempting to check the true positives, as due to rapid labor turnover only 5 of 10 positive subjects could be located for reexamination. Of these 5, 3 remained positive and 2 which were positive on first examination were negative at a later date. Thus it appears that in a given case examination may be positive for the sickle-cell trait at one time, at another time negative and that, therefore, in a group the apparent

incidence of susceptibility may be less than the real incidence, as some possessed of the trait may at the time of examination render a negative film. Some writers assert that in persons showing this phenomenon it is a constant finding, but the results of our check-up show that this is not uniformly the case. Anderson¹³ mentions an instance in which a patient showed no progressive sickling while in the hospital, but two weeks after his discharge showed from 90 to 95 per cent sickling in moist preparations twenty-four hours old.

Wassermann tests were not obtained except in 1 case, in which it proved to be negative. Hemoglobin estimation by the Tallqvist scale varied, but the lowest readings were 75 to 80 per cent. In 150 men, 10, or 6.63 per cent, of sickle-cell trait were found, which is in close agreement with the percentage reported from other localities. This indicates a similar incidence in healthy industrial workers and in hospital or dispensary patients, although it must be remembered that the personnel of this group did not include any women.

Conclusions. 1. The history, however important in other respects, is of little value in the detection of subjects with sickle-cell trait, but may be suggestive.

2. The physical signs are not diagnostic. Absence of scleral color anomalies or of lymph-node enlargement may possibly be regarded as evidence against the presence of the sickle-cell trait in any one individual.

3. Examination of moist blood films is a simple method of diagnosing the condition.

4. The percentage of the occurrence of the sickle-cell trait in 150 negro men applying for work was 6.67 per cent.

The accompany microphotograph was made by Dr. E. F. Cooke.

BIBLIOGRAPHY.

1. Hayem: Quoted in Editorial: Sickie-shaped Red Blood Cells, *J. Am. Med. Assn.*, 1929, 92, 2105.
2. Herrick, J. B.: Peculiar Elongated and Sickie-shaped Red Blood Cells in a Case of Severe Anemia, *Arch. Int. Med.*, 1910, 6, 517.
3. Archibald, R. G.: *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1926, 19, 389.
4. Sydenstricker, V. P.: *Med. Clin. North America*, 1929, 12, 1451.
5. Cooley, T. B., and Lee, P.: Sickie-cell Anemia in a Greek Family, *Am. J. Dis. Child.*, 1929, 38, 103.
6. Alden, H. S.: Sickie-cell Anemia: Report of Two Cases from Ohio Illustrating Its Hemolytic Nature, *Am. J. MED. SCI.*, 1927, 173, 168.
7. Browne, E. Z.: Sickie-cell Anemia, *Med. Clin. N. Am.*, 1926, 9, 1191-97.
8. Stewart, W. B.: Sickie-cell Anemia: Report of a Case With Splenectomy, *Am. J. Dis. Child.*, 1927, 34, 72.
9. Hahn, E. V.: Sickie-cell (Drepanocytic) Anemia, *Am. J. MED. SCI.*, 1928, 175, 206.
10. Bell, A. S., *et al.*: Sickie-cell Anemia: Two Cases with Splenectomy, *Am. J. Dis. Child.*, 1927, 34, 1923.
11. Smith, J. H., Jr.: Sickie-cell Anemia, *Med. Clin. North America*, March, 1928, vol. 11.
12. Cooley, T. B., and Lee, P.: The Sickie-cell Phenomenon, *Am. J. Dis. Child.*, 1926, 32, 334.
13. Anderson, H. B.: Sickie-cell Anemia, *Am. J. MED. SCI.*, 1926, 171, 641.

CHLOROTIC ANEMIA OF PREGNANCY.

A REPORT OF THREE CASES.

BY MAURICE B. STRAUSS, M.D.,

BOSTON.

(From the First Medical Service of the Boston City Hospital, Boston, Mass.)

SINCE the first American description of an anemia of pregnancy by Walter Channing,¹ in 1842, there have been many case reports of this condition with a variety of causative factors.

Alder,² in 1924, classified the anemias associated with pregnancy as follows: I. Anemia with pregnancy: (a) chlorosis; (b) post-hemorrhagic anemia; (c) congenital hemolytic icterus; (d) previously present primary pernicious anemia; (e) leukemia, acute or chronic; myelocytic or lymphocytic. II. Anemia from pregnancy: (a) physiologic; (b) pernicious type of anemia of pregnancy.

Larrabee,³ in 1925, divided his cases of anemia of pregnancy into a primary "pernicious" type and a secondary type.

O. H. P. Pepper,⁴ in 1929, called attention to the fact that most of the publications on the subject of pregnancy anemia antedated modern hematologic and investigative methods.

Recently, 3 cases of the "pernicious" type of anemia of pregnancy were reported in detail by Peterson, Field and Morgan.⁵ These cases all showed a "pernicious" type blood picture, but with free hydrochloric acid present in the gastric juice, and all recovered with liver therapy in exactly comparable manner to cases of Addisonian pernicious anemia not associated with pregnancy.

In striking contradistinction to these, the following 3 cases of "chlorotic" anemia of pregnancy all show a chlorosis-type blood picture with a complete and persistent achylia gastrica, and all show a quantitative response to iron therapy. In each of these the anemia definitely dated to the pregnancy and showed no tendency to recur afterward, but was otherwise exactly comparable to the chronic chlorosis described by Faber.⁶

Case Reports. CASE I.—M. L., Boston City Hospital, No. 599357: A married, white housewife, aged thirty-four years, was admitted on December 19, 1929, complaining of weakness. The family history was entirely negative. During childhood, the patient had had chicken-pox, measles, mumps and pertussis. At the age of ten, she had had chorea. At fourteen, she had had quinsy sore throat, and had had frequent attacks of tonsillitis well into adult life. For many years, she had had headaches, chiefly frontal, usually occurring in the late afternoon. She had been delivered of eight normal children, an anencephalic monster, and had had three miscarriages at from three to seven months. During the last six years she had had some shortness of breath on exertion, palpitation, occasional dizziness, and was quickly exhausted after slight exertion. At puberty she had had a nervous

breakdown of an unknown type. On December 4, 1929, she was admitted to the Boston Lying-in Hospital and on December 8 was delivered of a non-viable anencephalic monster. Delivery was complicated by a compound presentation and hydramnios, but there was no abnormal bleeding. On the following day she became wildly delirious and was transferred to the Boston Psychopathic Hospital where she remained until admission to the Boston City Hospital. A pale yellow color of the skin and a moderate anemia were noted upon the patient's admission to the Psychopathic Hospital. The mental condition cleared rapidly and in ten days the patient was well enough to be transferred from the institution.

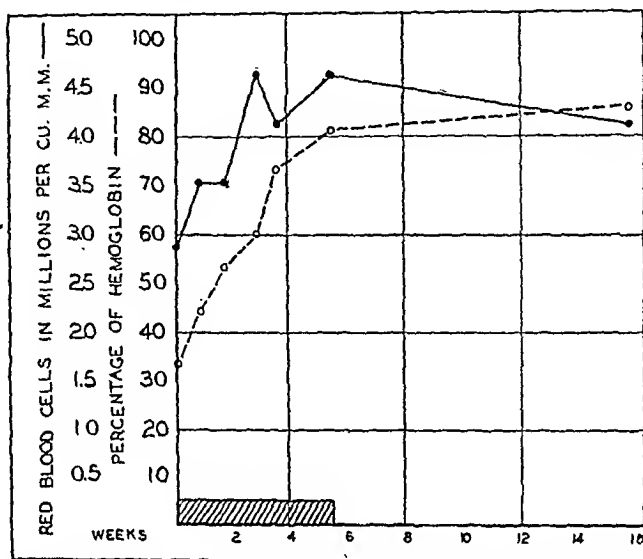


CHART I.—Case I. M. L. Cross-hatched area represents 6 gm. of iron and ammonium citrate daily.

On admission to the Boston City Hospital, it was noted that the patient was very pale and somewhat orthopneic. Oral sepsis and dental caries were present. The tongue was smooth and showed evidence of papillary atrophy about the margins. The heart was enlarged, the apex beat was in the fifth interspace, 10.5 cm. from the midsternal line. There was a mid-diastolic thrill at the apex and a loud systolic and short crescendo presystolic murmur at the apex. The systolic murmur was heard all over the precordium and was transmitted to the axilla. The second pulmonic sound was accentuated. The abdomen was lax; the uterus not felt. The reflexes, skin sensation, vibratory and position sense were all normal. The urine was of normal specific gravity, no albumin, no sugar; leukocytes and epithelial cells in the sediment. Stool was formed, brown; occult blood negative. Teleroentgenogram showed an enlarged heart. Electrocardiogram showed no abnormalities. Gastric analysis showed no free hydrochloric acid in the fasting contents or after an alcohol test meal, or after the subcutaneous injection of 0.5 mg. of histamin. The hemoglobin was 33 per cent (Sahli), red blood cells, 2,870,000; leukocytes, 8000. Stained smear showed abundant platelets, marked achromia, very slight anisocytosis and poikilocytosis. No abnormal white cells were seen. During the month in the hospital, the leukocytes varied from 6550 to 9500. The hemoglobin rose steadily until discharge, when it was 73 per cent and the erythrocytes were 4,100,000 (Chart I).

The only therapy administered was iron and ammonium citrate, 6 gm. daily. The diagnosis upon discharge was rheumatic heart disease, mitral stenosis and insufficiency, dental caries and chlorotic anemia of pregnancy.

Two weeks later the patient was seen, at which time the hemoglobin was 81 per cent, and red blood cells, 4,600,000. She was advised to discontinue further iron therapy. On April 11, 1930, she was again seen, at which time the hemoglobin was 86 per cent; red blood cells, 4,150,000; white blood cells, 7500. There was no achromia, anisocytosis or poikilocytosis seen in the stained smear. Gastric analysis at this time showed no free hydrochloric acid in the fasting contents, after an alcohol test meal or after 0.75 mg. of histamin subcutaneously. Pepsin and rennin content of the gastric juice were very low.

CASE II.—M. L., Boston City Hospital, No. 599380: A married, white housewife, aged twenty-five years, was transferred on December 20, 1929, from the obstetric service for treatment of anemia. The family and past histories were entirely negative except for the fact that the patient had considered herself "run down" after a twin pregnancy one and a half years before. Two weeks before transfer to the medical service, she had been delivered of a normal male child. This had been her second pregnancy. She had had no bleeding during it nor was there any evidence of dietary insufficiency, but during the last two months of the pregnancy she had noted that she was becoming increasingly pale and, occasionally, had had a sensation of pins and needles in her fingers.

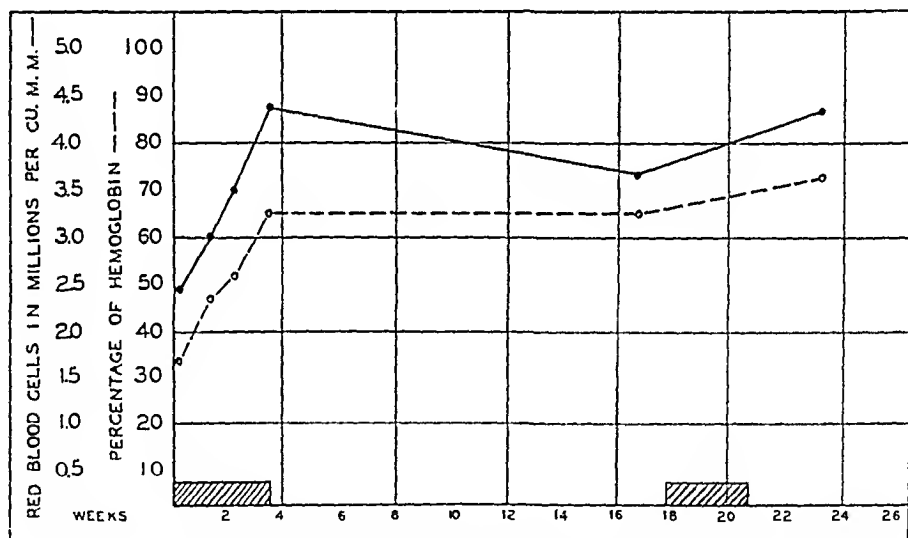


CHART II.—Case II. M. L. Cross-hatched area represents 6 gm. of iron and ammonium citrate daily.

Examination showed marked pallor of the skin and mucous membranes, a smooth tongue with evident marked papillary atrophy, and dental caries. The heart was enlarged to percussion with the apex 12 cm. to the left of the midsternal line, almost in the anterior axillary line. The first sound at the apex was blurred and was followed by a loud, rough systolic murmur. The second pulmonic was slightly accentuated. The abdomen was normal; the uterus not felt. The breasts were firm; the patient had not been permitted to nurse her baby. The reflexes, skin sensation, vibratory and position sense were entirely normal. The urine was of normal specific gravity with occasional traces of albumin on five of nine examinations, and occasional white cells in the sediment. The teleroentgenogram showed a heart enlarged transversely to the left. Electrocardiogram showed no abnormalities. Gastric analysis showed no free hydrochloric acid in the fasting contents, one hour after an alcohol test meal, or one-half hour after sub-

cutaneous injection of 0.5 mg. of histamin. The hemoglobin was 33 per cent (Sahli), erythrocytes, 2,450,000; leukocytes, 12,550. Stained smear showed increased platelets, marked achromia, very slight anisocytosis and poikilocytosis. No abnormal white cells were seen. During the stay in the hospital, the leukocytes varied from 6900 to 10,850. The hemoglobin rose steadily until discharge, three and a half weeks after admission, when it was 65 per cent and the erythrocytes were 4,380,000 (Chart II).

The only therapy administered was iron and ammonium citrate, 6 gm. daily. The diagnosis upon discharge was chlorotic anemia of pregnancy, and dental caries.

Three months later, on April 11, 1930, patient was again seen, at which time the hemoglobin was 64 per cent; erythrocytes, 3,650,000; leukocytes, 7300. Platelets appeared normal on smear. There was no achromia, anisocytosis or poikilocytosis. The gastric analysis at this time failed to show the presence of free hydrochloric acid in the fasting contents, after an alcohol test meal or after 0.75 mg. of histamin subcutaneously. Pepsin content was one-third the usual normal. Rennin content was very low. The patient stated that contrary to instructions she had not taken any iron after discharge. Six weeks later, on May 28, 1930, patient reported that she had taken iron and ammonium citrate, 6 gm. daily, for three weeks. The hemoglobin was 72 per cent; erythrocytes, 4,310,000; leukocytes, 8500. Stained smear showed very slight anisocytosis, otherwise it was normal.

CASE III.—M. McK., Boston City Hospital, No. 594840: A married, white housewife, aged twenty-four years, was admitted during the last month of her second pregnancy from the Pre-natal Clinic, because of her anemia. The family history was entirely negative. The past history included measles and pertussis in childhood, and cervical adenitis from the age of twelve years on. Three years before admission biopsy had been done which revealed tuberculosis. Under light therapy the glands had markedly subsided. Seven years before admission she had had a twin pregnancy in which she suffered from mild eclampsia. However, both children were living and well. During the present pregnancy she had noted an increasing pallor of the skin and there had been occasional slight edema of the ankles, palpitation and dyspnea. Appetite had been good. There was no evidence of dietary insufficiency.

Physical examination showed marked pallor of the skin and mucous membranes and dental caries. The tongue appeared normal. There were several matted firm glands in the left superior cervical chain and a linear scar of biopsy. The heart was of normal size to percussion. The first sound was somewhat roughened at the apex and followed by a soft systolic murmur. The second pulmonic sound was somewhat accentuated. The uterus was palpated just below the xiphoid. Fetal movements were active. The reflexes, skin sensation, vibratory and position sense were entirely normal. The urine was of normal specific gravity. There was no albumin or sugar present. Epithelial and white blood cells were seen in the sediment. Stools were formed, brown; negative for occult blood. Teleroentgenogram showed a normal sized heart. Gastric analysis on two examinations showed no free hydrochloric acid after an alcohol test meal, or one-half hour after the subcutaneous injection of 0.5 mg. of histamin. The hemoglobin was 35 per cent (Sahli), the erythrocytes, 3,530,000; leukocytes, 9550. The stained smear showed slightly diminished platelets and marked achromia. No abnormal white blood cells were seen. During the six and a half weeks in the hospital, the leukocytes varied from 7750 to 11,000. On the day of delivery, November 15, 1929, five weeks after admission, the hemoglobin had risen to 68 per cent; erythrocytes, 4,750,000. Eleven days after delivery, the hemoglobin had further risen to 78 per cent; erythrocytes, 4,810,000 (Chart III).

The only therapy administered from the day of admission until discharge after delivery was 6 gm. of iron and ammonium citrate daily. The diagnosis upon discharge was chlorotic anemia of pregnancy, tuberculous cervical adenitis, and dental caries.

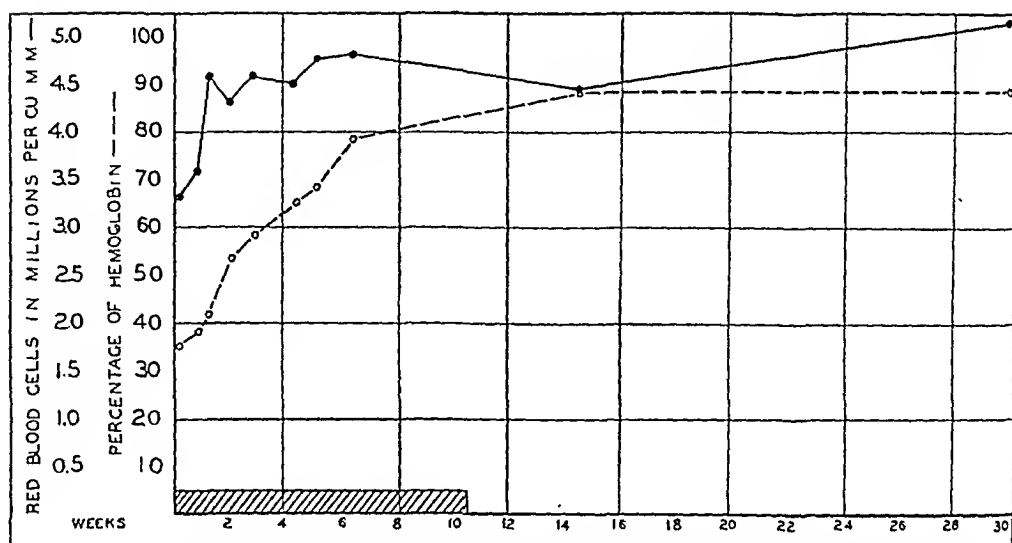


CHART III.—Case III. M. McK. Delivered at end of fifth week. Cross-hatched area represents 6 gm. of iron and ammonium citrate daily.

Two months later the patient stated that she had continued to take 6 gm. of iron and ammonium citrate daily for the first month after discharge. The hemoglobin was 88 per cent; erythrocytes, 4,410,000. The patient felt and appeared perfectly well. Four months subsequent to this visit, the patient was again seen at which time the hemoglobin was 88 per cent; erythrocytes, 5,210,000; leukocytes, 6720. The platelets on smear were normal in size and number; the white blood cells were normal; the red blood cells showed no achromia, no anisocytosis and no poikilocytosis. Gastric analysis at this time failed to show the presence of free hydrochloric acid in the fasting contents, after an alcohol test meal or after 0.75 mg. of histamin subcutaneously. Rennin and pepsin content of the gastric juice were very low. Lipase was completely absent.

Discussion. There are certain outstanding features in these 3 cases. All had a total achylia gastrica, including posthistamin specimens. This achylia is of very much less common occurrence than that after the usual test meals, which is itself rare enough in this age group. With the usual test meal, Smith⁷ found 1 of his 8 cases of pregnancy anemia to have an achlorhydria, Hoskin and Ceiriog-Cadle reported 1,⁸ Pepper 1,⁴ and Larrabee 1,³ but few such analyses have been made.

The blood picture in these 3 cases was typically that of chlorosis and, except for the fact that the anemia occurred with pregnancy, these cases are in every way comparable to the chronic chlorosis of Faber.⁶ The work of Mettier and Minot⁹ has suggested that this type of anemia is due to a conditioned iron deficiency in which

the achlorhydia presumably prevents the absorption of adequate amounts of iron from an ordinary diet, since they have shown that iron given therapeutically in an acid medium is more effective than when administered in a neutral or alkaline medium.

It is felt that in these 3 cases the diet furnished an adequate amount of iron, in spite of the possible faulty assimilation due to the achlorhydia, as long as there were no added demands upon the patients. Pregnancy, however, was just such an added burden, and until more iron was therapeutically added to the diet, anemia developed. As soon as iron was administered, hemoglobin was rapidly produced, stopping again when the administration of iron ceased, and, in Case II, again occurring when iron was ingested. Shulten¹⁰ and Larrabee³ have recently called attention to the value of iron in conditions of chlorosis and the work of Mettier and Minot has gone far in elucidating the mechanism of this deficiency.

In these 3 cases, the anemia definitely dated to the pregnancy, justifying the diagnosis of chlorotic anemia of pregnancy. It is believed, however, that any other added burden might well produce a similar anemia in patients with this anomaly of secretion, conditioning an iron deficiency.

Conclusions. 1. Three cases of chlorotic anemia of pregnancy are presented.

2. All 3 cases had a total achylia gastrica.

3. All 3 cases recovered on iron therapy alone.

4. It is believed that the added demands of pregnancy for hemoglobin resulted in an iron deficiency conditioned by the gastric achylia.

NOTE.—I wish to thank Dr. Ralph C. Larrabee for permitting me to publish the above cases.

REFERENCES.

1. Channing, W.: Notes on Anhaemia, Principally in Its Connections With the Puerperal State and With Functional Disease of the Uterus, With Cases, New England Quart. J. Med. and Surg., 1842, 1, 157.
2. Alder, A.: Beitrag zur Kenntnis der Anämien in der Schwangerschaft, Ztschr. f. Geburtsh. u. Gynäk., 1924, 87, 505.
3. Larrabee, R. C.: The Severe Anemias of Pregnancy and the Puerperium, AM. J. MED. SCI., 1925, 170, 371.
4. Pepper, O. H. P.: A Review of Our Knowledge of the Anemias of Pregnancy, Med. Clin. North America, 1929, 12, 925.
5. Peterson, R., Field, H., and Morgan, H. S.: Liver Treatment in the Pernicious Anemia of Pregnancy, J. Am. Med. Assn., 1930, 94, 839.
6. Faber, K.: Achylia Gastrica mit Anämie, Med. Klin., 1909, 5, 1310; Anämische Zustände bei der Chronischen Achylia Gastrica, Berl. klin. Wchnschr., 1913, 1, 958.
7. Smith, C. T.: An Anemia of the Puerperium, Surg., Gynec. and Obst., 1925, 40, 223.
8. Hoskin, T. J., and Ceiriog-Cadle, E.: A Case of Severe Anemia of Pregnancy Simulating Addison's Anemia, Lancet, 1927, 1, 433.
9. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastric Contents in Certain Cases of Anemia, J. Clin. Invest., 1929, 7, 510.
10. Shulten, H.: Zur Behandlung hypochromer Anämien mit maximalen Eisendosen, München. med. Wchnschr., 1930, 77, 355.

EPITUBERCULOSIS.

A STUDY OF TEN CASES FOR A PERIOD OF OVER TWO YEARS.

BY BENJAMIN GOLDBERG, M.D., F.A.C.P.,

AND

BENJAMIN M. GASUL, M.D.,

CHICAGO, ILL.

(From the City of Chicago, Municipal Tuberculosis Sanitarium and the University of Illinois, College of Medicine.)

UNTIL recent years, pulmonary tuberculosis in children was regarded as extremely serious or almost uniformly fatal. Until 1920, children under three years of age who, on physical and roentgenologic examination revealed massive areas of pulmonary disease were, in the presence of a positive tuberculin reaction, invariably given a poor prognosis.

Eliasberg and Neuland¹ were the first to demonstrate that this conception was erroneous. In 1920, these authors reported a series of tuberculous children with massive involvement as described. The children studied by them became, after a period of time, entirely free from physical or roentgenologic pulmonary findings. Originally they had all manifested a well-defined clinical disease syndrome and had shown physical findings with dullness involving usually one whole lobe of a lung, most frequently an upper lobe, associated with bronchial breathing and few or no râles.

The onset in the cases studied was subacute; there was little or no fever and the general physical condition of the patients was good. The cough was not prominent. The extensive pulmonary physical findings were, in every instance, altogether out of proportion to the mild aspect of the clinical picture. The massive dullness over a whole lobe of the lung, usually an upper lobe, associated with bronchial breathing, seemed, to the writers, rather extraordinary in view of the mild fever, slight cough and general benign appearance of the patient.

The roentgenologic examination revealed a heavy, homogeneous density over the whole or greater part of the affected lobe; the density was usually sharply demarcated from the rest of the lung. These roentgenologic findings remained constant, usually for weeks or even for months without abrupt change. Then, after varying periods, the physical findings—dullness and bronchial breathing—gradually disappeared, and the Roentgen ray showed a gradual diminution in the density of the affected lobe. Finally, all physical and roentgenologic evidence, with the exception of enlarged hilus glands and the positive tuberculin reaction disappeared. It is

important to note that throughout the course of the condition, the sputum examination was always negative for tubercle bacilli.

Eliasberg and Neuland differentiated this infection from both caseous tuberculous pneumonias and from chronic, nontuberculous pneumonias. The gelatinous, caseous, tuberculous pneumonia (Virchow's "glatte pneumonie") is differentiated by the acute onset, high fever and usually rapidly fatal end. The chronic, nontuberculous pneumonias were differentiated by the history, usually present, of an acute pneumonic onset or by the preliminary history of measles, influenza or other respiratory infection. In addition, the course of the chronic, nontuberculous pneumonias is attended by more severe constitutional disturbances and, usually, by physical findings of lower lobe involvement associated with many râles or evidence of fibrosis.

One of the cases reported by Eliasberg and Neuland, an eleven-month-old infant, who had previously shown a fairly typical massive involvement of the right upper lobe, died of an intercurrent bronchopneumonia and empyema. The autopsy showed no tuberculous change in the right upper lobe. Unfortunately, the pathologic report is incomplete and does not deal with the matter of the hilus gland.

According to Eliasberg and Neuland² the nature of these massive pulmonary involvements was a nonspecific infiltration on a specific tuberculous soil and they called the condition epituberculous infiltration.

Although Eliasberg and Neuland were the first ones to bring out the characteristic clinical and roentgenologic pictures of this lung affection, the French medical literature called attention to this type of lung involvement as early as 1883, when Grancher³ presented a similar clinical case and called it "splenopneumonia." Grancher considered his case as one of a subacute form of a bronchopneumonia. Bourdel⁴ in 1886, in his book, "De la Splenopneumonie," summarized the known facts regarding Grancher's splenopneumonia by characterizing it as a peculiar form of a subacute bronchopneumonia, similar microscopically to hypostatic congestion but differing from it in that it contained a sero-abluminous exudate in the alveoli, the physical findings of which were those of a pleurisy, a paracentesis thoracalis always giving negative results. The course was protracted, but usually offered good prognosis. The relationship of this splenopneumonia to tuberculosis was not known at that time.

Hutinel⁵ in 1911, was the first one in France to point out the frequency with which this splenopneumonia is associated with hilus tuberculosis. Sluka⁶ in 1912, described the triangular wedge-shaped infiltration around the hilus glands as characteristic of a tuberculous involvement. Ranke⁷ called the areas surrounding a tuberculous structure perifocal inflammations, Tendeloo,⁸ collateral

inflammation, and Fraenkel,⁹ gelatinous infiltration. Ribadeau-Dumas¹⁰ in 1919, described similar cases under the name of perituberculous infiltrations. Gravinghoff¹¹ in 1921, reported 3 additional cases of epituberculosis. One of his cases showed complete healing, the second one was still under observation, and the third case came to autopsy one year after the complete disappearance of the epituberculous infiltration of the right upper lobe. The autopsy revealed no tuberculous structures in the right upper lobe; the right hilus showed a calcified gland.

Engel¹² in the same year, reported a number of cases showing what he termed, "paratuberculous lung affections." Some of his cases showed decreased breath sounds over the infiltrate instead of bronchial breathing as reported by the other writers. He also observed cases with an acute onset and with high fever. Of the 3 cases that came to autopsy, one lung showed definite tuberculous involvement, the second case showed "fresh and old pneumonic foci," and the third case, clinically a typical case of epituberculosis, showed grossly no tuberculous structures. The histologic findings were, unfortunately, not given. All of these cases, however, showed a calcified or caseous gland in the hilus on the same side where the epituberculous infiltration was present.

The most important autopsy so far described was that of Epstein¹³ who, in 1922, published a typical case of epituberculosis that came to autopsy while the infiltration was still present. The autopsy, performed by Professor Gohn, revealed a large, caseous tuberculous primary focus in the cranial portion of the infiltrate, with many small tubercles surrounding it. There was atelectasis of the remainder of the affected lobe. The histologic examination failed to reveal tubercle bacilli in the atelectatic portions of the lung.

Langer¹⁴ in 1922, reported a typical case of epituberculosis in a child, aged four and a half years, who showed a dense, homogeneous shadow of the left upper lobe, which persisted for over nine months. Four and a half years later the child received $\frac{1}{10}$ mg. tuberculin intravenously which was followed by a high fever, pain over the left upper chest, and by physical and roentgenologic findings of massive pulmonary involvement of the same left upper lobe. This infiltration disappeared fourteen days later. Langer thought that this case proved the specific tuberculous nature of the so-called epituberculosis. Wimberger,¹⁵ Kleinschmidt,¹⁶ Bass and Wessler,¹⁷ Wagner,¹⁸ and Redeker¹⁹ reported additional cases in 1924 and 1926.

In the American medical literature, Gerstenberger and Burhaus,²⁰ in discussing ultraviolet therapy of extensive pulmonary tuberculosis in infants, reported 7 cases of massive pulmonary involvement—all of whom recovered. Some of their infants even showed roentgenologic evidences of large cavity formations. They exposed their patients to the quartz mercury arc at least three times a week and

it was their impression that they were benefited thereby. The experiences they obtained "forced them to agree with Kleinschmidt, Epstein, Gravinghoff, Engel and others that the clinical syndrome described by Eliasberg and Neuland for differentiating between a tuberculous or a nontuberculous massive pulmonary infiltration is not satisfactory or dependable." They even went so far as to state that "even cavitation might represent a stage of successful, specific immunologic process" of the body against the tubercle bacillus. Stoloff²¹ reported a case that most probably belongs to the type of epituberculosis. In 1929, one of us²² encountered 8 cases of epituberculosis in a follow-up study of 404 tuberculous infants.

Case Reports. During the last two years, we have been conducting a follow-up study in 500 tuberculous contacts and controls among the dispensary children of the Municipal Tuberculosis Sanitarium of the city of Chicago. We encountered 10 typical cases of epituberculosis among these children and we are briefly reporting our observations here.

CASE I.—J. M., colored, aged six years, apparently noncontact to tuberculosis. First seen at the dispensary on February 2, 1929. Chief complaint was poor appetite and a slight cough, especially at night. The patient had had measles and whooping cough; the family history was negative.

The essential physical findings were: Temperature, 100.6°; pulse, 108; respiration, 20. Weight, 47½ pounds; height, 47 inches. Increased vocal and tactile fremitus, with dullness and bronchial breathing over the entire right upper lobe. No râles heard at all. The tuberculin test (dermatubin²³) was strongly positive. Sputum examination for the tubercle bacillus was negative. The Roentgen ray revealed a dense, homogeneous shadow of the right upper lobe. No changes in the physical findings were noted for three months when the dullness and bronchial breathing began to disappear. Roentgen rays taken at monthly intervals showed a gradual absorption of the infiltrate. The general condition remained good throughout. The temperature, after the initial examination, did not go up above 99°, the appetite was good, and the patient gained 8 pounds in eleven months.

The Roentgen ray taken on October 9, 1929, showed an almost complete absorption of the infiltrate. On January 23, 1930, another tuberculin test (dermatubin) was performed and this was followed by a severe focal, local and general reaction. The physical findings were dullness and bronchial breathing over the entire right side of the lung, and the Roentgen ray examination showed a complete consolidation of the entire right lung. Serial Roentgen ray films, taken one week apart after this reaction, are now beginning to show areas of resorption in the involved right lung.

CASE II.—A. H., aged nine years, colored, apparently noncontact. First seen on April 24, 1929. Chief complaint, cough of few weeks' duration, very slight. Had had measles and diphtheria. Negative family history. Essential findings: Temperature, 99.6°; pulse, 106; respiration, 24. Weight, 50 pounds; height, 51 inches. Dullness and bronchial breathing over the right upper lobe. No moisture. Positive tuberculin test.

Roentgen ray examination showed massive involvement of the right upper lobe. Sputum examination negative for tubercle bacilli (10 times). The general condition of the patient remained good throughout our period of

observation. The patient gained 9 pounds in eleven months. There was a gradual diminution in the density of the area involved which is still progressively diminishing.

CASE III.—M. L., white, aged four years, child adopted at age of two years from St. Johns' Hospital, Springfield, Ill. Nothing known about the parents. Patient was sent in from the Children's Memorial Hospital as a case of pulmonary tuberculosis. First seen on May 17, 1928.

The essential findings: Temperature, 98.4°; pulse, 100; respiration, 22. Weight, 32½ pounds; height, 38¾ inches. The only lung findings noted were harsh breath sounds over the upper left lobe. The dermatubin test was strongly positive. Sputum examination negative for tubercle bacilli. Here again, the general condition remained good and the patient gained 7 pounds in seventeen months. The Roentgen ray plates showed a shrinkage of the tuberculous focus and a shadow density of the left upper lobe resembling that of a calcareous deposit.

CASE IV.—M. B., colored, aged three years. Contact to an open case of tuberculosis (mother) since birth. No complaints—entered the dispensary because mother died of tuberculosis one month previous. First seen on March 24, 1928.

Essential findings: Temperature, 98.6°; pulse, 94; respiration, 22. Weight, 32½ pounds; height, 37½ inches. Dullness and diminished breath sounds over the right upper lobe. Dermatubin test strongly positive. Sputum negative for tubercle bacilli. The patient was followed up until October 17, 1929, when she left the city. The highest temperature noted was 100.6°. Appetite was always good, and on October 17, 1929, her weight was 40 pounds, a gain of 7½ pounds in nineteen months. The Roentgen ray series shows a gradual absorption of the infiltrate going on to complete recovery.

CASE V.—J. B., colored, aged six years, apparently noncontact. Chief complaints: Poor appetite and cough of six weeks' duration.

Essential findings: Temperature, 99°; pulse, 100; respiration, 20. Weight 45 pounds; height, 42½ inches. Dullness of right lower lobe with diminished breath sounds. Dermatubin test strongly positive. Complement-fixation test, negative. Sputum examination negative for tubercle bacilli (15 times). The physical findings and the Roentgen ray films show a gradual absorption of the infiltrate, leaving a center of definite calcification.

CASE VI.—W. T., colored, aged nine years. Apparently noncontact. Chief complaints: Moderate cough of three months' duration. First seen on February 9, 1929.

Essential findings: Temperature, 98.6°; pulse, 118; respiration, 20. Weight, 57 pounds; height, 49½ inches. Dullness and bronchial breathing over the right upper lobe. Dermatubin test is strongly positive. Sputum examination negative for tubercle bacilli (4 times). The Roentgen ray shows a dense, homogeneous involvement of the right upper lobe which is still persisting. The patient's general condition is very good and the patient gained 6½ pounds in one year.

CASE VII.—S. A., aged two years, colored. Contact to an open case of tuberculosis (sister). No complaints. First seen on August 31, 1928.

Essential findings: Temperature, 97.8°; pulse, 100; respiration, 24. Weight, 23½ pounds; height, 32 inches. Dullness and bronchial breathing over the left upper lobe anteriorly. Very strongly positive dermatubin

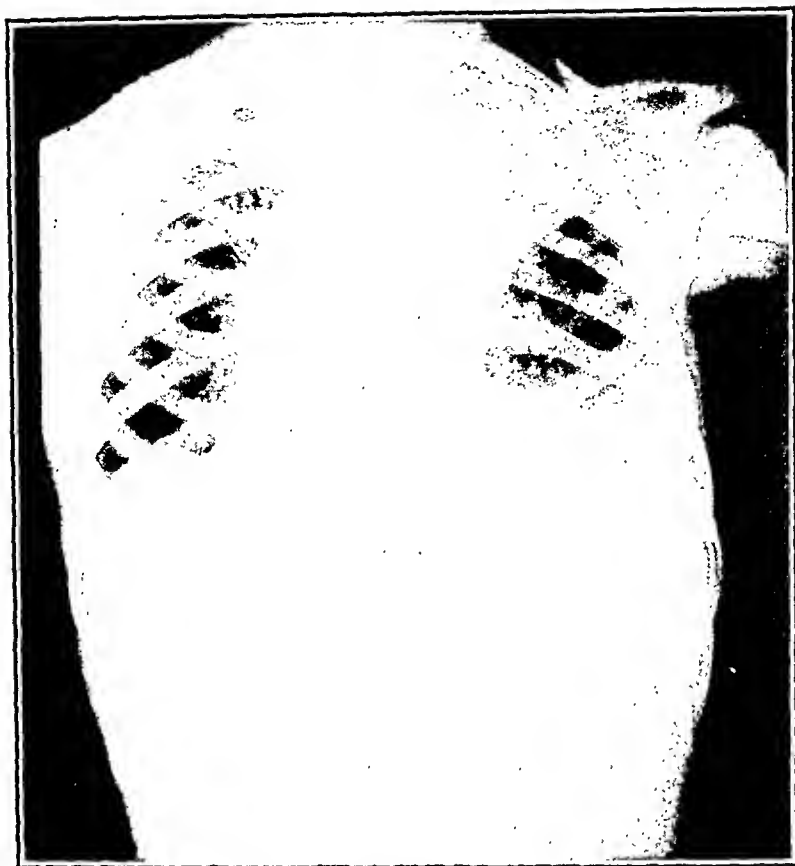


FIG. 1.—Case I. J. M., showing epituberculosis involving right upper lobe, April 27, 1929.



FIG. 2.—Case I. J. M., showing considerable resorption of the area of epituberculosis, October 7, 1929.



FIG. 3.—Case I. J. M., showing complete involvement of right lung after tuberculin (dermatubulin test), January 30, 1930.



FIG. 4.—Case II. A. H., Showing definitely demarcated areas of epituberculosis involving right upper lobe, May 21, 1929.

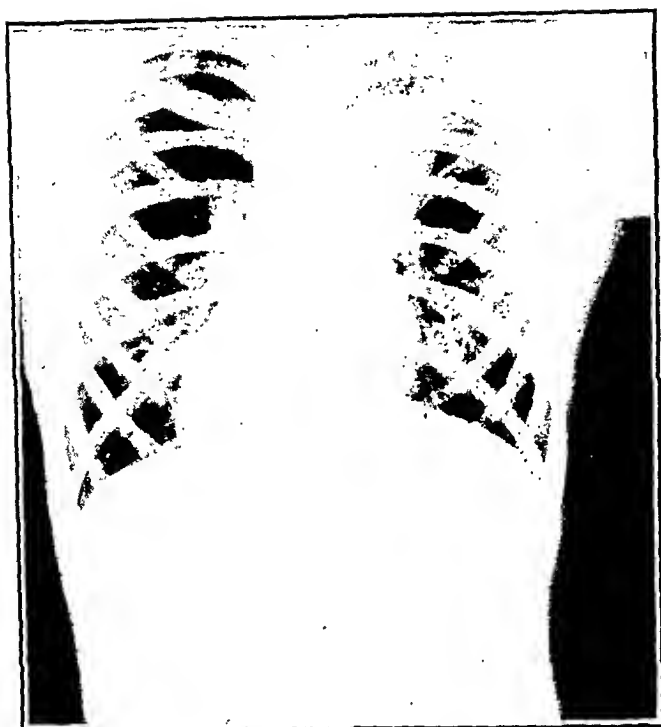


FIG. 5.—Case II. A. H., showing almost complete clearance of area previously involved March 20, 1930.

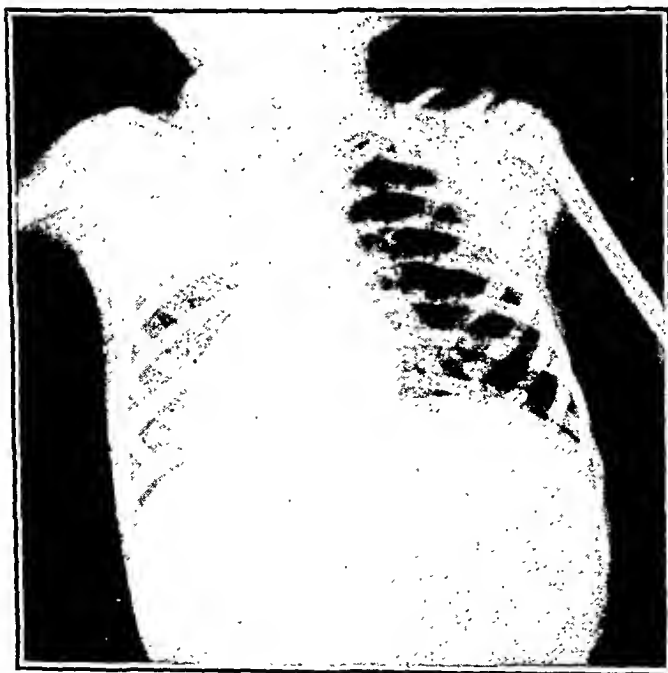


FIG. 6.—Case III. M. L., epituberculosis involving left upper lobe, May 19, 1928.

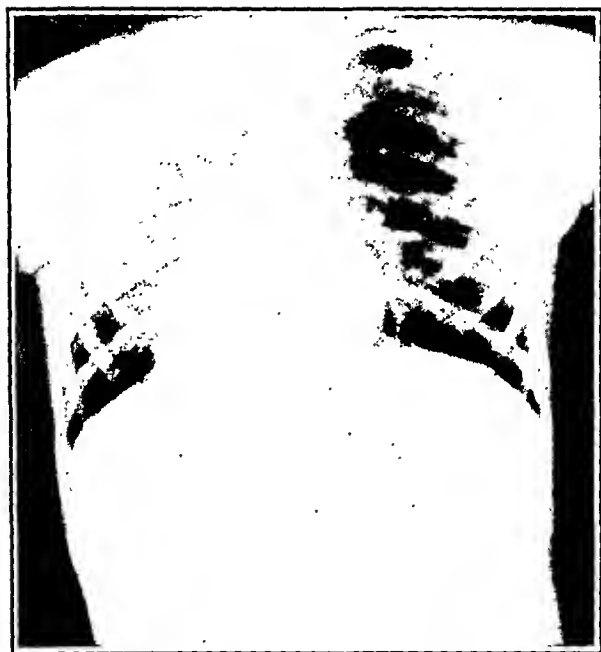


FIG. 7.—Case III. M. L., resorption of epituberculous involvement with shadow density resembling calcareous deposition, January 17, 1930.

test. Sputum negative for tubercle bacilli. The accompanying Roentgen rays show the gradual absorption of the infiltrate. The patient gained 7½ pounds in fifteen months, weighing 31½ pounds on January 30, 1930. The highest temperature recorded is 99° F., and the general condition has always remained good.

CASE VIII.—O. M., aged five years, colored. Noncontact. No complaints. First seen on February 26, 1927. Essential findings: Temperature, 99.6°; pulse, 112; respiration, 28. No definite pulmonary findings noted. Dermatubin test strongly positive. Sputum examination negative for tubercle bacilli (twice). The general condition remained good throughout our observation. The patient gained 3 pounds in one year.

CASE IX.—W. J., white, aged three years. Apparently noncontact. Chief complaint cough of about two months' duration. First seen on December 11, 1928.

Essential findings: Temperature, 98°; pulse, 100; respiration, 24. Weight, 34½ pounds; height, 39 inches. Dullness and bronchial breathing over the right upper lobe. Dermatubin test strongly positive. Sputum negative for tubercle bacilli. The Roentgen ray film shows dense, homogeneous involvement of the right upper lobe. The general condition was very good throughout the observation, patient gaining 3 pounds in four months. On April 23, 1929, patient developed measles, from which he recovered rapidly. Parents took the patient to California.

CASE X.—P. H., aged five years, white. Contact to mother who died of pulmonary tuberculosis two years ago. Chief complaint: Slight cough. First seen on July 6, 1928.

Essential findings: Temperature, 99.4°; pulse, 90; respiration, 20. Weight, 37¼ pounds. Dullness and bronchial breathing over the left upper lobe. Patient is the picture of perfect health. Dermatubin is strongly positive. Sputum examination is negative for tubercle bacilli. Roentgen ray film shows a shadow density involving the left upper lobe. The general condition remained good throughout the observation. Patient weighed 47¼ pounds on January 23, 1930, and the Roentgen rays show a gradual absorption of the infiltrate.

Comment. We have presented briefly the histories and findings of 10 typical cases of epituberculosis. Every one of these cases presented a picture originally described by Eliasberg and Neuland. The onset in our cases was never acute, there was very little fever, and the general condition of our patients was practically always good. All of our patients were ambulatory cases, and every one of them showed a considerable gain in weight during the time under our observation.

It was, indeed, very surprising to find massive pulmonary involvement in patients who oftentimes appeared in perfect health. All of our patients showed definitely positive tuberculin reactions, the sputum was always negative for tubercle bacilli and, in some cases, we examined the sputum on fifteen different occasions.

Our series of stereoscopic plates, showing at first dense homogeneous shadows involving a lobe of a lung, usually the right upper lobe,

and gradually clearing up, leaving in some cases no residue at all, and in others, calcified areas, complete the clinical description of epituberculosis. A study of the blood of our patients, as shown in Table I, gives no additional help in diagnosing this affection, while Table II shows the complement-fixation test for tuberculosis to be of absolutely no value.

TABLE I.—SHOWING THE AVERAGE RED BLOOD CELL, WHITE BLOOD CELL, AND DIFFERENTIAL COUNT IN OUR TEN CASES OF EPITUBERCULOSIS.

Case No.	Hemo- globin, per cent.	Red blood cells.	White blood cells.	Neutro- philes, per cent.	Small lymph, per cent.	Large lymph, per cent.	Mono- cytes, per cent.	Eosin, per cent.	Baso- philes, per cent.
1	65	3,760,000	16,300	79.5	9.0	3.0	7.7		
2	75	5,220,000	7,400	26.0	22.0	and myelocyte 0.5	14.0	2.5	
3	80	4,165,000	7,450	47.0	11.5	34.5	11.0	4.0	1.0
4	75	4,900,000	8,200	42.0	20.0	24.5	7.0		
5	78	4,390,500	9,265	47.0	32.5	31.0	9.5	4.0	0.5
6	82	5,060,000	6,150	36.0	35.5	6.5	5.0	8.0	
7	72	4,265,000	9,000	41.0	36.0	15.5	7.5	2.5	
8	78	4,270,000	9,250	67.7	9.5	13.0	4.5	2.5	0.5
9	84	5,020,000	13,500	37.5	5.5	16.0	3.5	1.5	
10	70	4,590,000	11,000	69.5	2.0	51.5	and myeloblasts 0.5	1.0	0.5
						20.0	7.0		

200 cells were always counted for differential. Dare method was used for hemoglobin.

TABLE II.—RESULT OF COMPLEMENT-FIXATION TESTS FOR TUBERCULOSIS IN OUR CASES OF EPITUBERCULOSIS.

Case No.	Results.
1	Negative
2	Negative
3	Test not performed
4	Negative
5	Negative
6	Negative
7	Negative
8	Negative
9	Positive
10	Negative

What is the nature of these infiltrations? Are they nonspecific as described by Eliasberg and Neuland, or do they represent specific tuberculous structures as believed by Gravinghoff, Langer, Gerstenberger and others? The autopsies performed do not definitely answer this very important question. The macroscopic and microscopic findings of the case of Eliasberg and Neuland were marked by the intercurrent empyema and bronchopneumonia, and were not reported in detail. The case of Gravinghoff died one year after the complete disappearance of the infiltrate and showed no tuberculous structures except for a calcified gland in the hilum on the affected side. One of Engel's cases showed definite tuberculous tissue but the clinical picture was not typical of epituberculosis. Another of his cases, clinically typical of epituberculosis, showed no tuber-

culous structures except for a calcified hilus gland. Epstein's case came to autopsy while the infiltrate was still present. The autopsy was performed by Professor Ghon and this case throws more light on the nature of the affection than any other case so far reported. The cranial portion of the infiltrate revealed a large caseous tuberculous primary focus, surrounded by many small tubercles. The remainder of the lung infiltrate was atelectatic and showed no tuberculous structures histologically.

Our Case I is unusual in that an infiltration of the whole of the right lung followed a tuberculin test after the original infiltrate had practically disappeared. This is the second case on record where the infiltrate reappeared following a tuberculin test. Our case differs, however, from Professor Langer's case in that the infiltrate, although now showing definite areas of absorption, is still present two months after the tuberculin test. The infiltrate, in our case, is progressing the usual, prolonged course of an epituberculous infiltrate. In Professor Langer's case the infiltrate disappeared within fourteen days. Our case and that of Professor Langer point most strongly to the infiltrate being intimately associated with the tubercle bacillus. It is at least a tuberculotoxic reaction on a specific tuberculous soil. Whether this infiltrate is histologically a tuberculous structure, or whether it consists of nonspecific inflammatory elements surrounding a tuberculous focus, or whether it represents an atelectatic portion of the lung due to the blockage of the return lymphatic circulation by a swollen tuberculous hilum gland or other focus, still remains an open question. Our clinical experience and the few autopsies reported in the literature seem to show that pathologically epituberculosis may, in some cases, represent a nonspecific, collateral inflammation, in others a large atelectatic area and, perhaps, in still others the infiltrate may be a definite tuberculous structure which may go on either to calcification or rarely to caseation and cavitation.

We feel that clinically these cases represent a definite entity, and in the great majority of cases, can be definitely diagnosed and differentiated from tuberculous pneumonias and chronic, nonspecific pneumonias. We feel that Eliasberg and Neuland deserve much credit for calling the attention of the medical profession to this type of lung affection, even though experience has shown that it is not always so easy to differentiate epituberculosis from tuberculous pneumonias. In the past, a tuberculous child with massive pulmonary involvement was always given the death verdict. Now we know that this massive pulmonary involvement oftentimes represents a beneficial, successful immunologic reaction of the body toward the destructive advances of the tubercle bacillus.

Conclusions. 1. Ten typical cases of epituberculosis in children have been studied clinically and roentgenologically for a period of about two years.

2. All of our cases were tuberculous children who presented massive pulmonary involvement, which either completely disappeared or is still undergoing resolution.

3. In one of our cases which had undergone resorption, an infiltration of the right lung followed a tuberculin reaction.

4. The epituberculous infiltrate is intimately associated with the reactions of the tubercle bacillus or of its toxins.

5. It is not clear whether the epituberculous area is a collateral inflammation or an atelectasis, the result of blockage of an enlarged hilum glandular process, or a truly tuberculous parenchymal involvement, or any of these in a given case.

NOTE.—The authors appreciate the assistance in the dispensary supervision of these cases by Drs. Harry H. Freilich, Saul Soloway and the late Dr. Joseph S. Cohn.

REFERENCES.

1. Eliasberg and Neuland: Die Epituberkulose Infiltration der Lunge bei Tuberkulosen Säuglingen und Kind, *Jahrb. f. Kinderh.*, 1920, **93**, 88.
2. Eliasberg and Neuland: Zur Klinik der Epituberkulose and Gelatinosen Infiltration, *Jahrb. f. Kinderh.*, 1921, **94**, 102.
3. Grancher: *Proceeding Société Médicale des Hôpitaux*, 1883, **8**, 13.
4. Bourdel: *De la Splenopneumonie*, Paris, 1886.
5. Hutinel: Les reactions broncho-pulmonaires dans les adenopathies mediastines, *Gas. des hôp.*, 1911, **84**, 76.
6. Sluka: Die Hilustuberkulose des Kindes in Roentgenbild., *Wien klin. Wehnschr.*, 1912, **7**, 140.
7. Ranke: Zur Diagnose des Rindlichen Tuberkulose, *München. Med. Wehnschr.*, 1914, **27**, 2099.
8. Tendeloo: *Allgemeine Pathologie*, Berlin, J. Springer, 1919, pp. 409 and 416.
9. Fraenkel: *Pathologische Anatomie*, Kaufman's I, p. 341, 1922, Berlin, V. W. V.
10. Ribaldeau-Dumes: Les reactions perituberculeuses die poumon de l'enfant, *J. de méd. et de chir. prot.*, 1919, **90**, 933.
11. Gravinghoff: Zur Kenntnis der Epituberkulose Infiltration, *Monatschr. f. Kinderh.*, 1921, **21**, 447.
12. Engel: Ueber Paratuberk. Lungenerkrankungen, Berlin, *Klin. Wehnschr.*, 1921, **31**, 877.
13. Epstein: Zur Klinik der Epituberkulose Infiltration der Rindlichen Lunge, *Jahrb. f. Kinderh.*, 1922, **97**, 99.
14. Langer: Die Spezifität Ruckbildungsfähiger Lungeninfiltrate bei der Rindlichen Tuberkulose, *Ztschr. f. Kinderh.*, 1922, **34**, 142.
15. Wimberger: *Verhand. d. Deutsh. Gesellsch. f. Kind*, *Monatschr. f. Kinderh.*, 1925, **29**, 409.
16. Kleinsehnidt: *Beit. z. Klin. d. Tuberk.*, 1926, **61**, 330.
17. Bass and Wessler: Die Besonderlichkeiten der Roentgen Thorax Diagnose in Kindesalter, *Jena*, 1924, p. 91.
18. Wagner: *Mitteil d. Gesell. f. inn. Med. u. Kinderh. in Wien*, 1926, **19**, 364.
19. Redeker: Ueber die exudative Lungeninfiltrate, *Beitz. z. Klin. d. Tuberk.*, 1926, **59**, 588.
20. Gerstenberger and Burhaus: Treatment of Extensive Pulmonary Tuberculosis with Ultraviolet Rays, *Am. J. Dis. Child.*, 1927, **33**, 54.
21. Stoloff: Acute Massive Ateleetasis of the Lung Complicating a Fresh Tubercular Primary Complex, *Am. J. Dis. Child.*, 1928, **35**, 239.
22. Gasul, B. M.: The Prognosis of Tuberculosis in Infants, *Am. J. Dis. Child.*, 1929, **37**, 909.
23. Goldberg, B. and Gasul, B. M.: A Comparison of the Dermatubin, Pirquet, Moro and Mantoux Tests. (To be published.)

THE PROTECTIVE POWER OF THE PLEURA.

BY MINAS JOANNIDES, M.S., M.D., F.A.C.S.,

ASSOCIATE IN SURGERY, COLLEGE OF MEDICINE, UNIVERSITY OF ILLINOIS, CHICAGO, ILL.

(From the Department of Surgery, College of Medicine, University of Illinois, Chicago.)

THERE is a striking similarity between the peritoneum and the pleura. This latter tissue has not as yet received its proper consideration. Both these tissues are morphologically related: They develop from a common ancestor. They cover the intrathoracic and intraabdominal organs and afford the necessary protection to these organs. Under normal conditions they prevent friction by the production of a lubricating fluid over the surface of each organ. In case of inflammation (be it bacterial, physical or chemical in origin) the peritoneum, as well as the pleura, produces a fibrinous exudate which patches the local injury and in more severe types it plasters the respective organ to an adjacent normal organ or the adjacent wall.

The lung is surrounded by the visceral pleura. One may consider the tissue as a part of the lung tissue. Actually, however, it is not related to the structure of the lung and acts only as a protective cloak. Under normal conditions it is made up of a few layers of cells and these have the power of preventing any leakage of air or fluids from the lung into the pleural cavity. This tissue is so thin and transparent that it makes a very useful window through which to watch the structure of the functioning lung. In certain species of lungs, as for instance the beef lung, where there is a great tendency to divide into lobules, the pleura is seen to extend into the interlobular space. In other species as the sheep, the dog, and to some extent in man, there is a lesser tendency to lobulation and the pleura appears as a uniform sheet covering the lung tissue. The pleura is apparently just merely attached to the lung because if the intraalveolar air pressure is raised to a point beyond the strength of cohesion between the lung and the pleura, the latter separates from the lung and forms an air bulla. If this increased pressure persists, the air will now undermine the bullous pleura and cause a greater separation. If this rise in intrapulmonic pressure is too rapid, the air bulla, instead of enlarging, will rupture and cause a pneumothorax. It requires a pressure of 60 to 100 mm. of mercury to produce this phenomenon. It can be produced by introducing the compressed air from a tank intratracheally or by the use of an air-tight mask attached snugly to the nose and mouth of the dog. The pleura limits the lung volume to a certain maximum. The lung tissue is very elastic and has a power of expansion much greater

than the total volume allowed for by the pleura. It is this reserve elasticity that allows the lung to stretch the pleura to a drumlike tension, and when a break occurs then the separated parts give way on either side of the rupture, allowing a lateral stretching of the lung but no herniation of the lung through the pleura. The pleura is so air-tight that even at a pressure of 100 mm. of mercury above atmospheric pressure no leakage of air occurs. Slight injuries to the lung such as needle pricks or small incisions are healed over without much discomfort to the subject. Following such a wound the lung-tissue juices promptly plug up the opening and the pleura promptly covers it over with new cells or induces an adhesion of this part of the lung to the chest wall. This protective power cannot be utilized if the wound has injured the larger bronchioles or larger vessels whereby a bronchial fistula or a severe hemorrhage may result.

The osmotic function of the pleura is quite important and applies primarily to the colloidal fluids present in the lung. These fluids usually do not pass through the pleural lining. Crystalloids, and water, on the other hand, may find their way into the pleural sac under two conditions, namely, the accumulation of a large amount of such a fluid and the increase of intraalveolar pressure. Water or normal salt solution may be used to fill up an extirpated lung with the heart attached to it. This water for the most part will find its way toward the lower lobe and will begin to appear much like perspiration on the surface of the pleura. This is probably the mechanism of transudation associated with chronic passive congestion of the lung in decompensation of the heart. When the intrapulmonic pressure is increased by injecting this water under pressure, drops of water accumulate very rapidly at the tip of the lung. Bloody fluids now are seen to come out under pressure from the severed systemic vessels leading to the heart or from the opened heart. The flow of the water is more noticeable when the pulmonary vessels are severed at a point before they enter the lung. When air is now blown into the lung at a pressure of 20 to 40 mm. of mercury, the flow of water continues from the vessels and the tip of the lung. In a few minutes the upper lobes begin to show crepitation and gradually the rest of the lung becomes air-containing. The process of forcing water out of the lung by increasing the intrapulmonic pressure is not similar to the expansion seen in a consolidated pneumonic lung where the intraalveolar exudate is colloid and contains fibrinous strands. This fibrin as it contracts, pulls the alveolar walls together and lessens the alveolar volume. The consolidation is due to the presence of exudate as well as the diminution of the volume of each alveolus due to the contraction of the fibrinous deposits. It is perhaps for this reason that with only a slight increased intrapulmonic air pressure (20 to 35 mm. Hg.) we can see the lung expand to its normal volume without any fluids leaking out through the pleura.

Another means of determining the water-tight effect of the pleura can be demonstrated by immersing a normal formalin-fixed lung under water. It will be noticed that water enters the lung only through the bronchi. If, however, the pleura is stripped off carefully so as not to expose any larger bronchioles, the water will run into the lung both from the bronchus and the exposed, capsule-free lung. One can squeeze such a lung to get all the residual air and then dip it in water. In a few minutes it will absorb enough of water to expand to its normal volume much in the manner of a sponge.

In inflammation of the lung the pleura plays the same protective rôle as the peritoneum in the abdominal cavity. A localized pleurisy is usually present in the region of the inflammatory reaction of the lung. If the inflammation is sufficiently extensive, adhesions usually form between the lung and the chest wall in an effort to localize the lesion by immobilizing that part, and in the case of perforation into the pleural cavity by preventing a pneumothorax or a general empyema. Pleurisy with effusion associated with pneumonia or respiratory influenza should be looked upon much in the same manner as that of general peritonitis. Here the protective power of the pleura is temporarily overcome and a tendency to localization occurs as soon as the virulence of the infecting organism is lowered or the patient's resistance is raised.

Summary. 1. The pleura and peritoneum are anatomically and physiologically related. They both act as protective cloaks of their respective organs.

2. Normally the pleura and peritoneum prevent friction by keeping in a state of lubrication the organs that they cover. Under pathologic conditions they tend to wall off the underlying infection by the production of adhesions.

3. The pleura is a water-tight and air-tight covering of the lung. It protects the lung from overdistention. It normally prevents fluids from going from the lung into the pleura and *vice versa*. Air is not allowed to escape from the lung into the pleura except when the pleural lining is injured.

4. An intrapulmonic air pressure of over 60 mm. of mercury will cause a separation of the pleura from the lung and result in an air bulla.

5. Pleural effusion associated with pneumonia or influenza may be regarded in the same light as peritonitis following gastrointestinal inflammation. There is a tendency on the part of the pleura to localize the lesion or protect the rest of the lung by the production of adhesions.

NOTE.—The author wishes to express his gratitude to Drs. W. F. Peterson, R. Jaffé, and S. Rosenthal, who so kindly furnished the necessary autopsy material for this study.

THE OCULAR MANIFESTATIONS OF SYMPATHETIC NERVOUS SYSTEM HYPERACTIVITY IN CONDITIONS OTHER THAN EXOPHTHALMIC GOITER AND ESPE- CIALLY IN ESSENTIAL HYPERTENSION.

"LIDSPASM:" A NEW EYE SIGN.

BY HARRY B. FRIEDGOOD, M.D.,

INSTRUCTOR IN MEDICINE, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.; FORMERLY
MEDICAL HOUSE OFFICER, THE PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.)

THE classical descriptions of exophthalmic goiter have considered exophthalmos and the eye signs with which it is customarily associated, as a frequent, although not necessarily a constant, phenomenon of Graves' syndrome. Little attention, however, has been directed to the fact that these ocular manifestations appear not only in exophthalmic goiter, but also in what seem to be, on superficial consideration, wholly unrelated clinical syndromes.

The apparent frequency with which exophthalmos and its associated eye signs were met in routine physical examinations of patients with hypertension and various conditions other than exophthalmic goiter prompted further investigation in this direction.

Historical. The historical aspect of this question which concerns itself with the mechanism involved in the production of these ocular phenomena, as well as with their occurrence in conditions other than Graves' syndrome, is an interesting one.

EARLY THEORIES. It was not long after the early descriptions of exophthalmic goiter that theories concerning the mechanism of its production were naturally considered. Of these, increase in retrobulbar fat and increased periorbital vascularity were most favored. Both of these theories had their advocates, but it was soon recognized that each had its limitations, some of them insurmountable.

The clinical observations that the degree of exophthalmos could vary in intensity from time to time in the same patient dealt the fatal blow to the hypothesis which considered an increase in retrobulbar fat as the essential feature. This knowledge, in spite of the relative frequency with which an increase in retrobulbar fat was demonstrated during postmortem examinations, soon established the latter as a manifestation of secondary importance complicating chronic exophthalmos.

Trousseau¹ (1865) and Filehne² (1879) were among the early advocates of the increased vascularity theory. In his experimental production of exophthalmos, Filehne² noticed that enucleation of normal eyes in rabbits was unattended by the profuse hemorrhage

which took place when a similar operation was performed on an exophthalmic eye; Trousseau¹ reasoned that the rapid development of exophthalmos in acute exacerbations of Graves' syndrome was dependent upon engorgement of the orbital bloodvessels.

ANATOMIC ASPECTS. This theory, in its turn, has given way to the explanation based on anatomic and physiologic data. This became possible after Müller,³ MacCallum and Cornell,⁴ and subsequently Landström,⁵ described the smooth muscle fibers which extend about the eyeball and are attached to the eyelids as well as the anterior orbital fascia. Müller³ (1885) described very briefly three groups of plain muscle fibers: one bridging over the infra-orbital fissure and one in each eyelid, running vertically from the fornices of the conjunctiva to the superior and inferior tarsal plates respectively. By means of dissection and histologic studies, MacCallum and Cornell⁴ (1904) were able to demonstrate a conical mantle of smooth musculature about the eyeball continuous anteriorly with the musculature of the lids, and forming abundant attachments about the margin of the orbit. This musculature then passed backward to end about the foramen, through which the optic nerve entered the orbit.

In reviewing Müller's work, Landström⁵ (1907) suspected the inadequacy of these muscles, both from their size and position, in being wholly responsible for the production of exophthalmos and the associated eye signs. This, together with the inadequacy of the existing theories, led Landström to a more intensive histologic study of the orbital contents. By means of serial sections in different planes, he demonstrated a well-developed cylinder of plain muscle arising from the septum orbitale anteriorly and inserted just posterior to the equator of the eyeball. The eye signs of exophthalmic goiter now became more readily explicable on the basis of the accumulated anatomic discoveries of Müller, MacCallum and Cornell, and Landström.

PHYSIOLOGICAL ASPECTS. It remained, however, for the experimental physiologist to point out conclusive evidence in favor of this mechanism for the production of exophthalmos and the associated eye signs; further proof of a similar character was suggested by experience in the surgery of cervical sympathetic ganglia and by analogy with a characteristic clinical syndrome (Horner).

Exophthalmos has been produced experimentally on numerous occasions. The earliest attempt is recorded by Filehne² (1879), who originally produced it by incision or cauterization of the upper quarter of the inner portion of the corpora restiformia; Bienfait⁶ (1890) was able to confirm Filehne's observations with further experimental lesions of the restiform bodies. Additional evidence of a similar nature was offered by Mendel⁷ (1892), who reported a postmortem examination in exophthalmic goiter which revealed an atrophy of one restiform body.

As one would expect, the smooth musculature of the orbit (Müller, MacCallum and Cornell, and Landström) is abundantly innervated by the sympathetic nervous system, and its state of tonicity is constantly maintained by the latter. On the basis of this knowledge, Bernard⁸ (1862), Benard⁹ (1882), Langley and Sherrington¹⁰ (1891) and Jonnesco¹¹ (1900) demonstrated the production of exophthalmos and widened palpebral fissures by means of stimulation of the cervical sympathetics, and reported their results unequivocally. MacCallum and Cornell⁴ (1904) contributed important and substantial observations of a similar character. After removing the roof of the orbit and the orbital fat in dogs, they found that electrical stimulation of the cervical sympathetics produced great exophthalmos. During the experiment they observed peristaltic waves passing backward throughout the tissue surrounding the eyeball, and subsequent studies (*vide supra*) revealed the smooth musculature responsible for the peristaltic waves, exophthalmos and widened palpebral fissures. By further ingenious experiments, they demonstrated that the exophthalmos produced by cervical sympathetic stimulation was entirely independent of vascular bed changes in the orbit and directly dependent upon sympathetic nervous system stimulation of the smooth musculature. In 1915 Cannon, Binger and Fitz¹² reported unmistakable exophthalmos resulting from phrenicosympathetic anastomosis in cats and, although subsequent attempts to confirm this experiment have been unsuccessful, the original positive results are worthy of serious consideration.

CLINICAL ASPECTS. In 1865 Trousseau¹ emphasized the relation of the superior cervical sympathetic ganglion to the production of exophthalmos, and Edmunds¹³ (1895) later advocated extirpation of the superior cervical sympathetic ganglion for the relief of distressing exophthalmos. Subsequent surgery (Jaboulay,¹⁴ Jonnesco,¹⁵ Balacescu,¹⁶ Kocher¹⁷ and Mayo¹⁸) substantiated the practicability of Edmund's original suggestion.

The clinical syndrome (Horner) occasionally found complicating fractures of the cervical vertebræ with injury to the cervical sympathetics, and a similar condition produced experimentally (Langley and Sherrington,¹⁰ 1891), by sectioning the cervical sympathetic cord, is characterized by enophthalmos, pseudoptosis and myosis. Special sympathetic vasomotor disturbances usually accompany these changes, and all of them are obviously dependent upon interference with the activity of the sympathetic nervous system.

EYE SIGNS OF SYMPATHETIC NERVOUS SYSTEM HYPERACTIVITY. The available evidence, therefore, points to hyperactivity of the sympathetic nervous system as the factor responsible for the production of exophthalmos through spasm of the smooth muscles described by Müller, MacCallum and Cornell, and Landström. In the same way, the eye signs frequently found associated with exophthalmos or alone in exophthalmic goiter are no doubt produced

by means of a similar mechanism (von Graefe,¹⁹ Landström⁵). Although von Graefe recognized the coördination which normally exists between movements of the upper eyelid and the eyeball when the axis of vision is elevated or depressed, he pointed out only those instances in exophthalmic goiter (von Graefe¹⁹) where he noted failure of the upper lid to follow the downward movement of the eyeball. Subsequently, Kocher²⁰ (1910) described the retraction of the upper lid when the patient looked intently at an object. Referring to exophthalmic goiter and disturbances of innervation of the eyelids "in the domain of reflex activity . . . and of the arbitrary movements of coördination," Stellwag²¹ (1873) writes that "to the first category belongs one of the most constant symptoms usually present from the beginning, namely, the wide opening of the interpalpebral fissure and the incompleteness and rarity of the rhythmic movements of the lids. The gaping of the palpebral fissure is usually so large that quite a wide zone of sclera is exposed above and below the corneal margin. The rhythmic movement of the lids is often entirely absent for several minutes, is also generally very incomplete and is replaced by a slight drawing inward and by a weak, screwlike rotation of the edge of the lid. This symptom, in connection with the wide opening of the palpebral fissure gives to the physiognomy of the patient the peculiar hardness and staring appearance which is mentioned by so many authors."

In speaking of the action of the levator palpebræ superioris, Dalrymple²² (1834) states that "Its action is to raise the upper lid, to uncover the globe of the eye by drawing the tarsal cartilage beneath the margin of the orbit and at the same time it slightly protrudes the globe. In this last action it indirectly depresses the lower eyelid, inasmuch as the protrusion of the globe causes the lower lid to slide off its anterior convexity, and thus opens the eye to a greater extent, as in the act of staring." A modification of the latter in the form of inequality of the palpebral fissures has been reported, but its relative frequency has never been emphasized.

Lidspasm: A New Eye Sign. There remains one other eye sign to which reference has not been made hitherto. Its value lies in the fact that it is often present when the von Graefe is absent, although not necessarily positive when the von Graefe can be elicited. It is determined in a manner similar to that for the von Graefe, but in the reverse manner. After the patient watches the object reach the lowest point of the arc and the von Graefe sign has been completed, the object retraces its former path, in the upward direction. The upper eyelid is now retracted in advance of the moving eyeball, and a rim of white conjunctiva appears above the cornea if the "lidspasm" sign is positive. In some cases the rim of white conjunctiva does not appear, but there is sufficient dissociation of movement between the upper eyelid and the eyeball to designate the eye sign positive. Judging from the character of the new eye

sign and the manner in which it is elicited, its mechanism appears to be similar to that suggested for the von Graefe, and would, therefore, be dependent upon hyperactivity of the sympathetic nervous system with spasm of the smooth muscle in the upper eyelid.

CLINICAL MATERIAL AND PROCEDURE. The surprising frequency with which exophthalmos and its associated eye signs were met in routine physical examinations of patients with hypertension, obviously not suffering from exophthalmic goiter, prompted further investigation in this direction.

The Medical Out-door Department of the Peter Bent Brigham Hospital was particularly well suited to this type of work. Patients of every description are examined routinely, and in reality represent a cross-section of illness in adults of limited financial means. By far the largest amount of data was gathered on the female medical service and only a negligible small per cent of males were included.

Only 494 patients of the total number examined were eligible for this clinical study. All instances in which the thyroid gland might possibly be considered a complicating factor were automatically omitted. A sufficient number of basal metabolism determinations were carried out and found normal in the more difficult instances where the intensity of the symptoms and signs were of such a nature as to make exophthalmic goiter a distinct possibility. The surprising number of these determinations which were either normal or unusually low led to further study concerning the significance of exophthalmos and the associated eye signs of sympathetic nervous system hyperactivity.

This study, therefore, included 258 consecutive cases of essential hypertension, and 236 consecutive patients without hypertension were included to form some basis for relative comparison. Each patient was examined routinely, and special note made of age, clinical diagnosis, blood pressure and eye signs. The latter included bilateral and unilateral exophthalmos, von Graefe, Kocher, inequality of palpebral fissures, unequal pupils and the new eye sign "lidspasm." All doubtful signs were reported negative.

It was found that inequality of palpebral fissures could be determined accurately on inspection if note was made of the anatomic relation of the margin of the upper eyelid to the upper margin of the pupil. Exophthalmos was not measured by an exophthalmometer, but was determined by inspection. It was found by experience that unilateral exophthalmos was invariably accentuated if the patient looked in the upward direction. In the latter position, protrusion of the lower one-half of the eyeball became relatively more marked on the affected side. It is with full cognizance of the limitations in accuracy, dependent upon the personal equation, that the observations on exophthalmos are submitted. A colleague made an independent observation in a large number of the examinations, and only those cases which were substantiated in this manner are reported positive for either unilateral and bilateral exophthalmos

or unequal palpebral fissures. And finally, it was discovered that the von Graefe and lidspasm signs were more likely to be elicited with the patient in the vertical than in the horizontal position. In some instances they could be made to disappear by simply changing the patient from the former position to that of the latter.

CLINICAL DATA. The clinical data, gathered in this manner, has been summarized in the following paragraphs.

Hypertension is most prevalent in the sixth decade, and there is little significant difference in age frequency among those with or without eye signs. The peak of the curve for patients without hypertension (correlating frequency and age) lies in the fifth decade. Further, it is obvious that those without eye signs are by far in the majority in the group of patients without hypertension and that eye signs appear at an earlier age than in the group of patients with hypertension:

Age.	Per cent of 258 patients with hypertension.		Per cent of 236 patients without hypertension.	
	With eye signs.	Without eye signs.	With eye signs.	Without eye signs.
10+	0.0	0.38	1.60	6.7
20+	0.0	0.38	3.30	13.9
30+	1.9	1.10	4.60	19.0
40+	10.8	11.20	5.00	24.5
50+	15.1	20.60	5.00	8.8
60+	17.0	12.00	0.08	4.2
70+	2.7	5.80	0.00	1.2
80+	0.7	0.00	0.00	0.0

Of 258 patients with hypertension examined, 125 (44 per cent) had one or more of the eye signs mentioned above, with the exception of bilateral exophthalmos, which is reported independently (*vide infra*). Among 236 patients without hypertension, 49 (21 per cent) had one or more of the same eye signs.

Among the patients with hypertension the eye signs occurred in 29 different combinations and the number of eye signs in a single individual varied from one to five:

	Per cent of 125 patients with eye signs.	Per cent of all with hypertension (258).
70 patients had 1 (70 eye signs)	56.0	23.2
34 patients had 2 (68 eye signs)	27.0	13.1
10 patients had 3 (30 eye signs)	8.0	3.8
7 patients had 4 (28 eye signs)	5.6	2.7
4 patients had 5 (20 eye signs)	3.2	1.5
Total number of eye signs, 216.		

In the group without hypertension there were nineteen different combinations of the eye signs, and the number in a single individual also varied from one to five:

	Per cent of 49 patients with eye signs.	Per cent of all without hypertension (236).
33 patients had 1 (33 eye signs)	67.3	13.9
10 patients had 2 (20 eye signs)	20.4	4.2
4 patients had 3 (12 eye signs)	8.1	1.6
1 patient had 4 (4 eye signs)	2.0	0.04
1 patient had 5 (5 eye signs)	2.0	0.04
Total number of eye signs, 74.		

Bilateral exophthalmos was found about three times as frequently among patients with hypertension (15.5 per cent) as compared with individuals without hypertension (5.9 per cent). In the former it was associated with combinations of other eye signs in 8.9 per cent and in the latter in 2.5 per cent of the cases.

The frequency with which the individual signs occurred in patients with hypertension are tabulated as follows—the relative frequency of each eye sign was especially emphasized by the fact that each patient might have two or more in various combinations:

Signs.	Number recorded in 258 patients with hypertension.	Per cent of 125 patients with eye signs.	Per cent of all with hypertension (258).
Unequal palpebral fissures	73	58.0	28.2
Unilateral exophthalmos	38	30.2	14.7
Von Graefe	36	28.4	13.7
Kocher	36	28.4	13.7
Lidspasm	26	20.4	10.0
Unequal pupils	7	5.6	2.7
<hr/>			
Total number of eye signs	216		

Unilateral exophthalmos was found associated with a wide palpebral fissure on the same side in 24 of these cases.

Among the patients without hypertension the frequency with which the individual eye signs of sympathetic nervous system hyperactivity appeared, occurred as follows:

Signs.	Number recorded in 236 patients without hypertension.	Per cent of 49 patients with eye signs.	Per cent of all (236) without hypertension.
Unequal palpebral fissures	22	44.0	9.3
Von Graefe	16	32.6	6.7
Unilateral exophthalmos	11	22.4	4.6
Lidspasm	10	20.4	4.2
Kocher	10	20.4	4.2
Unequal pupils	5	10.2	2.1
<hr/>			
Total number of eye signs	74		

Unequal palpebral fissures are, therefore, the most common, and unequal pupils the least frequent of all eye signs in both groups.

The relative frequency of eye signs seems to be directly proportional to the degree of systolic hypertension. Blood-pressure readings were grouped in the following manner for statistic and illustrative purposes:

Blood pressures.	Per cent of 125 patients with hypertension and eye signs.	Per cent of 133 patients with hypertension but without eye signs.
$\frac{200+}{100=}$	41.0 (52 patients)	28.5 (38 patients)
$\frac{140 \text{ to } 198}{100+}$	22.4 (28 patients)	24.0 (33 patients)
$\frac{140 \text{ to } 198}{100-}$	36.0 (45 patients)	46.6 (62 patients)

If the eye signs are grouped individually according to the pressures with which they were found associated in the 125 patients with hypertension, it is evident that unequal palpebral fissures and unequal pupils are most often detected with the lower pressures. In spite of the fact that there is a decided predominance of patients with systolic blood pressures below 200, the remaining eye signs (unilateral exophthalmos, von Graefe, Kocher and lidspasm) show a marked tendency to appear associated with blood pressures whose systolic level is above 200:

Blood pressure.	Unequal palpebral fissures, per cent.	Unilateral exophthalmos, per cent.	Von Graefe's sign, per cent.	Kocher's sign, per cent.	Lidspasm sign, per cent.	Unequal pupils, per cent.
$\frac{200+}{100+}$	17.6	14.4	14.4	12.0	9.6	1.60
$\frac{140 \text{ to } 198}{100+}$	12.0	8.0	3.2	4.8	4.0	0.08
$\frac{140 \text{ to } 198}{100-}$	24.8	11.2	11.2	10.4	6.4	3.20

The patients with hypertension as well as those without hypertension who were examined on more than one occasion revealed the remarkable manner in which these sympathotonic signs could appear and disappear again on subsequent examinations. An example is abstracted at this point. This patient, with a definite history of hypertension, was seen on seven consecutive visits to the Out-door Department of the Peter Bent Brigham Hospital. Her general state of nervous tension seemed to have more relation to the intensity and number of the eye signs than did her blood-pressure level:

Date.	Blood pressure.	Eye signs.
Nov. 27, 1929	190/105	Von Graefe; bilateral exophthalmos.
Dec. 11, 1929	210/110	Von Graefe; bilateral exophthalmos; unequal palpebral fissures.
Dec. 23, 1929	152/80	Bilateral exophthalmos; unequal palpebral fissures.
Dec. 30, 1929	196/110	Von Graefe; lidspasm; Kocher; bilateral exophthalmos; unequal palpebral fissures.
Jan. 6, 1930	170/110	Von Graefe; Kocher; bilateral exophthalmos; unilateral exophthalmos, right, unmistakable; unequal palpebral fissures.
Jan. 13, 1930	188/92	Von Graefe; bilateral exophthalmos.
Jan. 18, 1930	180/100	Bilateral exophthalmos.

The diagnoses which represented the clinical condition of the 49 patients without hypertension but with eye signs are outlined at this point. The striking preponderance of the diagnosis "neurasthenia," the occurrence of so many patients with hypotension

and the relatively large number of neurologic and arthritic conditions seem worthy of special note.

- 24 with neurasthenia (functional disease); 6 had hypotension.
- 6 with chronic atrophic arthritis; 1 had hypotension.
- 5 with hysteria; 1 had hypotension.
- 4 with petit or grand mal; 2 had hypotension and 1 had duodenal ulcer.
- 2 with postencephalitic Parkinson's syndrome; 1 had hypotension.
- 2 with pulmonary tuberculosis; 1 had hypotension.
- 2 with duodenal ulcer; both had hypotension.
- 1 with primary familial muscular atrophy; also had hypotension.
- 1 with diabetes mellitus; also had hypotension.
- 1 with paroxysmal auricular fibrillation.
- 1 with hypotension.

A systolic blood pressure constantly below 110 mm. was considered a hypotension. Seventeen patients (35.6 per cent) of those with eye signs had clinical hypotension. Only 13 per cent had hypotension in the group without eye signs.

Discussion. At the present state of our knowledge certain facts are known concerning the anatomic distribution of the sympathetic nervous system and the signs and symptoms of its hyperactive state. The latter may be expressed either subjectively or objectively. The subjective manifestations include various types of nervousness, palpitation, emotional and vasomotor instability (peripheral vasoconstriction and dilatation). The objective signs of sympathetic nervous system hyperactivity may be detected through its influence on tonicity of musculature (tremor), cardiac rate (tachycardia), secretion of the sudoriferous glands (sweating) and the ocular manifestations of exophthalmos, lidlag, lidspasm, Kocher's sign and Dalrymple's sign.

A syndrome consisting of these signs and symptoms may be termed sympathotonia for convenience of reference. One must recognize, however, that as a general rule the latter is just a partial manifestation of a more profound autonomic disturbance. Although relief of the subjective manifestations are of immediate importance to the patient, he may well exaggerate their discomfort. It is the objective findings which point with reasonable accuracy to the actual state of tonicity and activity of the sympathetic nervous system.

During the course of this investigation, which was directed principally at the eye signs of sympathotonia, several broad generalizations naturally suggested themselves.

The most obvious of these was the widespread evidence of sympathotonia. Its occurrence in exophthalmic goiter has been

accepted as classic as well as a usual, although by no means constant, part of the syndrome. However, the intensity and frequency with which the eye signs of sympathotonia occurred in essential hypertension was apparently unsuspected, and its recognition suggested the possibility of a fundamental sympathetic disturbance common to both maladies.

The occurrence of exophthalmos in conditions other than exophthalmic goiter, and independent of mechanical production, was first reported by Sattler²³ (1885) in 3 cases. He pointed out its "symptomatic importance as an occasional attendant of hemorrhagic forms of retinitis occurring in connection with altered and increased general arterial pressure, the result of cardiac, renal and hepatic lesions." A slightly more extensive report of 16 cases of chronic nephritis was offered by Barker and Hanes²⁴ (1909). They found:

Von Graefe positive in 68.7 per cent of 16 cases.

Stellwag positive in 81.3 per cent of 16 cases.

Moebius positive in 43.7 per cent of 16 cases.

Unequal pupils in 31 per cent of 16 cases.

Albuminuric retinitis in 50 per cent of 16 cases.

They further noted that there was a coincident decrease in exophthalmos with a decrease in blood pressure, and believed that the hypertension as well as the exophthalmos were due to the same cause rather than dependent on each other. Our own observations seem to substantiate this opinion. In commenting upon this report, Thayer²⁴ confirmed the data presented by Barker and Hanes from his own clinical experience.

This new conception, of a sympathetic disturbance common to both exophthalmic goiter and hypertension, seemed of still greater significance when it was found that 21 per cent of patients without hypertension had a similarly hyperactive sympathetic nervous system. This observation proved of value in two ways: First, in corroborating an extensive literature and, in particular, the findings of Kessel and Hyman,²⁵ concerning the existence of a sympathotonic group of individuals (which they termed "autonomic imbalance") characterized by the signs and symptoms of a hyperactive sympathetic nervous system, indistinguishable from exophthalmic goiter, in association with a normal basal metabolism. Twenty-nine of these 49 patients without hypertension were apparently of this group, and heretofore diagnosed "neurasthenia" and "hysteria." Second, from another point of view, the reactions of this type of individual were in reality an expression of a hypertonic sympathetic nervous system, and, therefore, not "functional" in the ordinary sense of the word.

The second generalization is in the nature of a corollary to the first. The value of any sign or symptom in the differential diagnosis of a disease lies not only in the frequency with which it occurs

in that disease, but in the infrequency with which it is found in other conditions. The ocular manifestations of sympathotonia are obviously of little significance in the differential diagnosis of exophthalmic goiter, judging from the frequency with which they are met in essential hypertension, chronic nephritis with hypertension and individuals of sympathotonic tendencies. This evidence of sympathotonia is of importance, however, because it is one of the few objective findings which indicate the actual state of tonicity and activity of the sympathetic nervous system from time to time and because it gives us some insight into the possibility of a more fundamental disturbance than has been suspected hitherto.

A third conclusion, which is obviously of significance, is the state of flux in the tonicity of the sympathetic nervous system which is suggested by our observations. It has been known for many years that exophthalmos may vary in intensity during the course of exophthalmic goiter with successive remissions and exacerbations. Ample evidence has been accumulated during our work to corroborate this statement, and to extend it to include the other eye signs of sympathotonia. The rhythmic increase and decrease in these signs of sympathetic nervous system hyperactivity may be at least another objective manifestation of the partial remissions and exacerbations which have been encountered in the nervous signs and symptoms of exophthalmic goiter, hypertension and sympathotonic individuals.

Study of the patients without hypertension but with sympathotonia reveals a fourth factor concerning the association of this condition with disease of the nervous system. Its occurrence in hysteria, epilepsy, primary familial muscular atrophy and post-encephalitic Parkinson's syndrome is of some interest, and the nature of its relation to these conditions certainly deserves further study.

Special emphasis should be placed on the relative frequency with which sympathotonia was detected in chronic arthritis. Tangible evidence has already been offered in the literature on the relation of the sympathetic nervous system to arthritis. Rowntree and Adson²⁶ (1929) have reported an unusual case in which sympathetic ganglionectomy and ramisectomy resulted in a remarkable remission in an advanced arthritis deformans of crippling proportions.

Finally, it seems of importance to recognize the relation which seems to exist between the mechanism of blood-pressure maintenance and the presence of sympathotonic tendencies. Hypotension was three times as frequent among patients without hypertension with eye signs as compared with those without eye signs. The frequency of eye signs in patients with hypertension has already been pointed out and seems unequivocal. Apparently the mechanism responsible for blood-pressure maintenance, whatever its fundamental nature, may be accompanied by sympathotonia and vary in intensity without reference to the tonicity of the latter.

Summary. 1. The history of exophthalmos and the eye signs with which it is often associated is considered from their anatomic, physiologic and clinical aspects.

2. The eye signs of sympathetic nervous system hyperactivity are specifically defined, and quotations are recorded from Stellwag, von Carion and Dalrymple in an effort to clear up the confusion in the literature concerning their eye signs.

3. Lidspasm, probably dependent upon sympathetic nervous system hyperactivity, has been described as a new eye sign and its significance is discussed.

4. The eye signs, hitherto considered classic of exophthalmic goiter, have been noted with surprising frequency in conditions other than Graves' syndrome (neurasthenia, chronic atrophic arthritis, hysteria, petit or grand mal, postencephalitic Parkinson's syndrome, pulmonary tuberculosis, duodenal ulcer, primary familial muscular atrophy, diabetes mellitus, paroxysmal auricular fibrillation and hypotension) and especially in essential hypertension.

5. This clinical study includes 494 patients, of which 258 consecutive cases had essential hypertension and 236 consecutive patients had a normal blood pressure or a hypotension.

6. The influence of position on the detection of lidlag and lidspasm is emphasized; methods for accentuating unilateral exophthalmos and examining for inequality of palpebral fissures are recorded.

7. The clinical data which are presented include: (a) The age frequency of essential hypertension and eye signs. (b) The relation of essential hypertension to the occurrence of various eye signs. (c) The remarkable manner in which eye signs appear and disappear on subsequent examinations. (d) The relative frequency of the individual eye signs.

8. The subjective and objective signs of a hyperactive sympathetic nervous system are indicated, and for convenience of reference are termed "sympathotonia."

9. Several broad generalizations naturally suggested themselves during the course of this investigation. (a) The widespread evidence of sympathotonia (exophthalmic goiter, essential hypertension, chronic nephritis with hypertension *et cetera*). (b) The ocular manifestations are of little value in the differential diagnosis of disease, but of great importance in indicating, objectively, the actual state of tonicity in the sympathetic nervous system. (c) The state of flux in the tonicity of the sympathetic nervous system with tendencies to remissions and exacerbations, as detected in the appearance and disappearance of the eye signs, is emphasized. (d) Attention is directed to the relation which seems to exist between the mechanism of blood-pressure maintenance and the presence of sympathotonia. The relative frequency of hypotension in patients with eye signs is pointed out and its significance is discussed.

There is in existence a syndrome clinically indistinguishable from exophthalmic goiter, with the exception of the fact that the

basal metabolism is normal. It is characterized by various significant combinations of the cardinal and accessory signs and symptoms of Graves' syndrome.

I am indebted to Dr. Henry A. Christian for the privilege of carrying out this clinical investigation and for his many valuable suggestions. My thanks are also due to Dr. George E. Shambaugh, Jr., for his aid in confirming and checking up on many of the eye signs.

BIBLIOGRAPHY.

1. Trousseau, A.: Du goitre exophtalmique ou maladie de Graves, Clinique médicale de l'hôtel dieu de Paris, 1865, 2, 458.
2. Filehne, W.: Zur Pathogenese der Basedow'schen Krankheit, Sitzungsberichte der physik.-med., Societät zu Erlangen, 1879, 2, 177.
3. Müller, H.: Ueber einen glatten Muskel in der Augenhöhle des Menschen und der Säugethiere, Ztschr. f. wissenschaft. Zool., 1858, 9, 541.
4. MacCallum, W. G., and Cornell, W. B.: The Mechanism of Exophthalmos, Med. News, 1904, 85, 732.
5. Landström, J.: (1) Ueber Morbus Basedowii, Thesis, Stockholm, 1907; reviewed in J. Am. Med. Assn., 1909, 52, 476. (2) Exophthalmic Goiter, According to Modern Views, Almänna svenka Läkaretidning, 1908, No. 48; abstracted in Ophthalmology, 1909, p. 675.
6. Bienfait, A.: Contribution à l'étude de la pathogenie du goitre exophtalmique, Bull. de l'Acad. roy. de méd. Belgique, 1890, 4, 470.
7. Mendel, E.: Zur pathologischen Anatomie des Morbus Basedowii, Deutsch. med. Wehnschr., 1892, 18, 89.
8. Bernard, C.: Des phénomènes oculopupillaires produits par la section du nerf sympathique cervical; ils sont indépendants des phénomènes vasculaires calorifiques de la tête, Compt. rend. de l'Acad. d. sc., 1862, 55, 381.
9. Benard, H.: Contribution à l'étude du goitre exophtalmique, pathogenie, traitement, Thèse de Paris, 1882.
10. Langley, J. N., and Sherrington, C. S.: On Pilomotor Nerves, J. Physiol., 1891, 12, 278.
11. Jonnesco, T.: Physiologie du nerf sympathique cervical chez l'homme, Sect. physiol., XIII Cong. Internat. de Méd., Paris, 1900, p. 26.
12. Cannon, W. B., Binger, C. A. L., and Fitz, R.: Experimental Hyperthyroidism, Am. J. Physiol., 1915, 36, 363.
13. Edmunds, W.: Observations and Experiments on the Pathology of Graves's Disease, Trans. Path. Soc., London, 1895, 46, 224.
14. Jaboulay, M.: De la régénération du goitre extirpé dans la maladie de Basedow et la section du sympathique cervical dans cette maladie, Lyon méd., 1896, 81, 389.
15. Jonnesco, T.: Traitement chirurgical du goitre exophtalmique, XI Cong. Français de chir., 1897, p. 284.
16. Balacesev: Die totale und bilaterale Resection des Sympathicus cervicalis beim Morbus Basedowii, Arch. f. klin. Chir., 1902, 67, 59.
17. Kocher, A.: Ueber Morbus Basedowii, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1902, 9, 1.
18. Mayo, C. H.: The Surgical Treatment of Exophthalmos, J. Am. Med. Assn., 1914, 58, 1147.
19. Von Graefe, A.: Ueber Basedow'sche Krankheit, Deutsch. Klin., Berlin, 1864, 16, 158.
20. Kocher, T.: Zur Frühdiagnose der Basedow'schen Krankheit, Corr.-Bl. f. schweiz. Aerzte, 1910, 40, 177.
21. Stellwag, von Carion, C.: Treatise on the Diseases of the Eye (translated from the fourth German edition), 1873, p. 521.
22. Dalrymple, J.: The Anatomy of the Human Eye, London, 1834, p. 266.
23. Sattler, R.: Exophthalmus, Arch. Ophthal., 1885, 14, 190.
24. Barker, L. F., and Hanes, F. M.: Exophthalmos and Other Eye Signs in Chronic Nephritis, Trans. Assn. Am. Phys., 1909, 24, 146.
25. Kessel, L., and Hyman, H. T.: II. The Clinical Manifestations of Disturbances of the Involuntary Nervous System (Autonomic Imbalance), Am. J. Med. Scr., 1923, 165, 513.
26. Rowntree, L. G., and Adson, A. W.: Polyarthrititis: Further Studies on the Effects of Sympathetic Ganglionectomy and Ramisection, J. Am. Med. Assn., 1929, 93, 179.

REVIEWS.

THE PHYSIOLOGY OF THE VESTIBULAR APPARATUS. By MARIO CAMIS. Translated and Annotated by R. S. CREED, B.M., B.CH., M.A. Pp. 310; 65 illustrations. New York: Oxford University Press, 1930. Price, \$7.50.

THIS translation of Camis' monograph should prove extremely valuable to English readers who are unable to read the Italian original; and useful even to those familiar with Italian, since the translator has added many comments in which the statements of the original text are considered in the light of recent work by the Sherrington school. Written and translated by pupils of Sherrington it reviews the whole field of labyrinthine physiology, particularly in its relation to reflex activities. The historical aspects are fully treated; the functional disabilities resulting in animals from labyrinthine injuries are carefully described, including the somewhat neglected field of the effects of labyrinthine stimulation on the circulation, a field in which Camis himself has specialized.

The work of Magnus and de Kleyn is adequately covered as well as the interesting work of Schmaltz on the mode of stimulation.

Rotatory tests of labyrinthine function in man are treated shortly and without emphasis on their importance to aviation. While the view expressed that too much emphasis has been paid to the duration of nystagmus in estimating flying efficiency is sound, the importance of forced movements and wrong estimates of position following excessive labyrinthine stimulation in aviation has not been given here enough attention.

An excellent bibliography is included.

H. B.

MANUAL OF PHYSIOLOGY. By H. WILLOUGHBY LYLE, M.D., B. S. (LOND.), F. R.C.S. (ENG.), and DAVID DE SOUZA, M.D., D.Sc. (LOND.), F.R.C.P. (LOND.). Pp. 820; 138 illustrations, 3d edition. New York: Oxford University Press, 1930. Price, \$5.25.

THE compilation of a manual of physiology for medical students by a consulting surgeon and physician might appear to be an ideal arrangement, but in practice is a failure. This work may contain more physiological information than is possessed by the average

teacher of medicine but it provides a very inferior foundation for the medicine of the future. It is regrettable that the Oxford University Press has undertaken its publication, and that students' lack of judgment has resulted in its appearing in a third edition. While many sections of physiology are outlined with reasonable accuracy, the work can in no way be said to provide an adequate basis for the medicine of the future. For instance respiratory methods of measuring circulation rate receive no attention; the isolation of pitocin and vasopressin from pituitrin is not mentioned; the relation of the pituitary gland to the reproductive cycle is neglected; nystagmus of labyrinthine origin is assigned to interference between cerebellar and cerebral responses. This method of authorship is as successful as would be the writing of manuals of physics or medicine by professors of physiology.

H. B.

SURGICAL DIAGNOSIS, VOL. II. By 42 American Authors. Edited by EVARTS AMBROSE GRAHAM, A.B., M.D. Pp. 871; 834 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$35.00, set of 3 volumes.

VOLUME II is a worthy follower of its fellow. The first 128 pages are given over to Gynecologic Diagnosis written by Curtis. This section is really a text in itself. Each portion is well illustrated and followed by a short bibliography.

The section on Diseases of the Face, Mouth and Jaws by Blair, and others, is overlapped to some extent by the following discussions on Diseases of the Neck by Forrester and Raine. Copher and Dick give a rather condensed section on the Thyroid and Parathyroid glands and a fairly complete bibliography.

The surgical Diseases of the Stomach and Duodenum are treated by Horsley and Horsley. They give an excellent section on the anatomy and physiology of these organs, and discuss the diagnosis as it can be made from the history, physical findings and laboratory examinations. The technique of the laboratory tests is briefly outlined. The place of the Roentgen-ray in the diagnosis of these diseases is well emphasized and illustrated by outline drawings.

Hertzler has written the section on the Diseases of the Peritoneum, and the chapter on Diseases of the Appendix, Small and Large Intestines is by Richardson. The discussions of the diagnosis and complications of appendicitis and of intestinal obstruction are excellent.

Pool and Stillman have followed their comprehensive monograph in the preparation of their section on the Spleen. The diagnosis of Hernia is given by Fisher and Cole. Full discussions are given

as to the etiology, signs and symptoms of the common and rarer forms. The last chapter on the Diagnosis of Abdominal Emergencies by Allen of necessity includes a discussion of many subjects already described. It should prove one of the most valuable chapters for quick reference as an aid in making a differential diagnosis.

MEDICINE MONOGRAPHS. VOLUME XVII. EPHEDRIN AND RELATED SUBSTANCES. By K. K. CHEN, and CARL F. SCHMIDT. Pp. 121. Baltimore: The Williams & Wilkins Company, 1930.

A MONOGRAPH giving the history of ephedrin with a critical review of the clinical and pharmacologic literature, most of which has accumulated since this drug was reintroduced into occidental medicine by the authors. The information contained is not yet available in textbooks of pharmacology or therapeutics. The comprehensive nature of this review (the bibliography contains over 500 titles), and its concise form make it important for those who wish to employ the drug, but who have no time to study the original articles bearing upon its action and usefulness. I. S.

A COMPILATION OF CULTURE MEDIA. By MAX LEVINE, PH.D., and H. W. SCHOENLEIN, M.S. Pp. 969. Baltimore: The Williams & Wilkins Company, 1930. Price, \$15.00.

THE book is well printed and serviceably bound. It was "prepared at the request of the Society of American Bacteriologists, and financed by a grant from the Digestive Ferments Company."

The subject matter comprises directions for the preparation of 2543 different culture media, with their variants, which would comprise most, if not all, the recognized media in use for the cultivation of microorganisms.

The Reviewer has been unable to find any errors in the formulæ, nor omissions of useful media from the compilation.

The various media are classified according to their physical characters into seven groups, and by their clinical constituents into some forty or more sections.

There are four indices according to Medium Name, Constituents, Use, and Author, making it possible to find quickly any formula desired.

This work represents an enormous amount of painstaking labor, and should fill a useful place in every bacteriologic laboratory.

F. L.

HANDBOOK OF THE VACCINE TREATMENT OF CHRONIC RHEUMATIC DISEASES. By H. WARREN CROWE, D.M., B.CH. (OXON.), M.R.C.S., L.R.C.P. Pp. 52. New York: Oxford University Press, 1930. Price, 80 cents.

ANY book which claims to prove that the use of vaccines should make the prevention of chronic rheumatic diseases easy and allow every medical man to be in a position to treat his own rheumatic patients with a very fair measure of success is capable of doing much damage in the present state of our knowledge of this disease. If the only treatment in use at the Charterhouse Rheumatism Clinic is that by stock vaccines, it is natural that its director should be enthusiastic; perusal of his book, however, does not bring the conviction which he implies would be afforded by an ocular demonstration at his Clinic. We object to his basic but unproved and frequently opposed hypothesis that all rheumatic diseases are bacterial in origin, we are suspicious of views that are at times based on evidence that might be otherwise construed and often are expressed in incautiously enthusiastic terms, and we regret the almost complete absence, even in a book of this small size, of objective data to support rather sweeping claims. E. K.

A TEXT-BOOK ON ORTHOPEDIC SURGERY. By WILLIS C. CAMPBELL, M.D., F.A.C.S. Pp. 705; 507 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$8.50.

THOUGH not exhaustive Campbell's text-book is extremely well done. The arrangement of material is good and the relative space allotted to the various subjects is well proportioned.

That the treatment of fractures should be the work of the orthopedic surgeon is now accepted but it seems improper and almost futile to attempt to cover so vast a subject in the limited space of a single volume devoted to orthopedics in general.

The bibliographies appended to the various subchapters, are not extensive but for the most part well selected. The volume is strongly recommended as a text-book for students. G. W.

TEXT-BOOK OF HISTOLOGY. By ALEXANDER A. MAXIMOW, Completed and edited by WILLIAM BLOOM. Pp. 833; 604 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$9.00.

FOR some years before his death in 1928 Professor Maximow was engaged in the preparation of a text-book of histology. To his colleague Professor Bloom has fallen the task of completing the

work, which has just appeared. Professor Bloom has had the coöperation of the staff of the anatomical department of the University of Chicago, and the result is an important addition to American textbooks of histology. To all students of blood-formation and connective tissue cells Professor Maximow's brilliant researches are well known, and it is the parts of the book dealing with these topics that are most characteristic. In the chapters on blood, connective tissue proper, blood-forming and blood-destroying tissues, and spleen the illustrations are mostly original. They either appear now for the first time, or they are taken from Maximow's previous publications. In other chapters the figures are mostly taken from the works of others, some from special monographs, also many from the textbook of Schaffer. The latter is the case notably in the chapters on the special senses. The tissues of the nervous system are treated in eleven short chapters, chiefly by Professor Herrick. There is no description of cerebral or cerebellar cortex, or other regions of the brain. Under the heading of histophysiologic remarks, there is constant reference to function, though, of course, the description of structure is the main consideration. In practically every chapter there is a short account of the histogenesis of the tissue or organ being described. No technique is included, but a limited number of references is usually given at the end of a chapter. The book will be of interest to physiologists and pathologists as well as to anatomists.

W. A.

APHASIA IN CHILDREN. By ALEX W. G. EWING, M.A., PH.D., with an introduction by E. D. ADRIAN, M.D., F.R.C.P., F.R.S. Pp. 152. New York: Oxford University Press, 1930. Price, \$3.50.

EWING found that of 10 cases of "aphasia" in childhood, manifesting either absence of or gross defects in speech and language, 6 showed a marked, binaural lack of hearing for ascending orders of frequency in sound above 256 v.d. This deficiency was associated with normal or relatively normal hearing for sounds of frequency below 256 v.d. He showed that this lack of auditory acuity for the higher frequencies of sound had abolished the characteristic differences of the sounds of speech for these patients. He reached the very interesting conclusion that these cases showed no trace of the defects characterizing aphasia, and that in their speech and language development these cases passed through the same stages as the normal child. The tests made in Ewing's work were all done by the audiometer and were carefully controlled. The results indicate that the defect in these high-frequency deaf children may be in the cochlea, along the auditory path, or possibly even to late

myelination of the nerve fibers associated with hearing. Ewing prefers to use the term linguistic retardation for the type of case which he describes, rather than congenital aphasia. It is possible to educate these children to recognize sounds of the higher vibration frequencies.

The monograph is an interesting contribution. Its value is two-fold: the discovery of a type of case hitherto looked upon as an incurable aphasia, and the working out of a systematic method of testing hearing through its various ranges. The latter has led to the discovery noted, and should be carried out systematically in adult cases of aphasia as in the cases reported by Ewing. The book is a real contribution and can be recommended highly to otologists, neurologists, and all those interested in speech. B. A.

PERNICIOUS ANEMIA. By LEYBOURNE STANLEY PATRICK DAVIDSON, B.A. (CAMB.), M.D., F.R.C.P.E., and GEORGE LOVELL GULLAND, C.M.G., LL.D., M.D., F.R.C.P.E. Pp. 203; 30 illustrations. St. Louis: The C. V. Mosby Company, 1930. Price, \$8.50.

A CRITICAL summary of the various aspects of the pernicious anemia problem is of especial interest today, when so many new and important observations have been made as to its manifestations and efficacious treatment, without as yet solving the problem of its real nature. The authors have very ably accomplished their task of presenting such a review, based on a wise selection from the rather plethoric literature on the subject; and also have not hesitated to express their own views derived from a considerable experimental and clinical experience with the disease.

The opening historical chapter presents four periods: (1) Addison's and the British clinical observations; (2) Biermer's and the German widening and popularizing of the concept; (3) the contributions of Hunter, Ehrlich and others to pathologic and hematologic knowledge of the disease; (4) the past decade with its increased knowledge of blood formation and blood destruction and especially the invaluable discovery of liver as a therapeutic agent.

Following a good description of the pathologic anatomy of the disease comes a lengthy discussion of bacteriology, including the reproduction in full of a paper by one of the authors. As the results of this paper were wholly of a negative character, the general conclusions (p. 63) and the original reference would seem to have been sufficient.

In the discussion of etiology (p. 102 *et seq.*), the German view, that the disease is primary in the bone marrow as a disorder of blood formation, is preferred by the authors to Hunter's (and the

English) view that the primary site is in the gastrointestinal tract with a hypothetical hemolytic agent. The Reviewer has pointed out elsewhere that the therapeutically active liver substance of Minot (and now the gastric extracts of Castle) point to a deficiency nearer the primary source of the trouble than are the phenomena either of excessive blood destruction or abnormal blood formation. That the authors themselves recognize the importance of these etiological relationships is shown by their thorough discussion of the unknown specific factor necessary for normal blood formation (p. 110 *et seq.*).

Adequate further chapters on symptoms, blood and metabolic changes, diagnosis, prognosis and treatment and an appendix on dietotherapy complete the presentation, which we consider as the best review of a subject about which much has recently been written.

E. K.

BOOKS RECEIVED.

NEW BOOKS.

- Selected Readings in the History of Physiology.** Edited by JOHN FARQUHAR FULTON, M.D. Pp. 317; 61 illustrations. Springfield, Ill.: Charles C. Thomas, 1930. Price, \$5.00.
- Stalkers of Pestilence.** By WADE W. OLIVER, M.D. Introduction by THEOBALD SMITH, M.D., PH.D. Pp. 251; 23 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$3.00.
- History of Haitian Medicine.** By ROBERT P. PARSONS. Foreword by EDWARD R. STITT. Pp. 196; 21 illustrations and map of Haiti. New York: Paul B. Hoeber, Inc., 1930. Price, \$2.25.
- The Candiru.** By EUGENE WILLIS GUDGER, PH.D., with a Foreword by ALFRED SCOTT WARTHIN, PH.D., M.D., LL.D. Pp. 120; 18 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$1.50.
- Histology for Medical Students.** By H. HARTRIDGE, M.A., M.D., Sc.D., M.R.C.P., F.R.S., and F. HAYNES, M.A. Pp. 369; 512 illustrations. New York: Oxford University Press, 1930.
- Laboratory Medicine.** By DANIEL NICHOLSON, M.D. Pp. 433; 108 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$6.00.
- An Introduction to Malariology.** By MARK F. BOYD. Pp. 437; 82 illustrations. Cambridge, Mass.: Harvard University Press, 1930. Price, \$5.00.
- A Text-book of Pathology.** By E. T. BELL, M.D. Pp. 627; 316 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$8.00.
- Practical Midwifery for Nurses.** By BETHEL SOLOMONS, M.D., F.R.C.P.I., M.R.I.A. Pp. 354; 136 illustrations. New York: Oxford University Press, 1930. Price, \$2.75.
- Outline in Obstetrics for Nurses.** By F. W. RICE, M.D. Pp. 228; 56 illustrations. St. Louis: The C. V. Mosby Company, 1930. Price, \$2.00.
- La Rate, Organe Réservoir.** By LEON BINET. Pp. 116; 17 illustrations. Paris: Masson et Cie, 1930. Price, 20 Fr.

* Reviews of titles followed by an asterisk will appear in a later number.

The Edwin Smith Surgical Papyrus being Vols. III and IV of the University of Chicago Oriental Institute Publications, Vol. I, Hieroglyphic Transliteration Translation and Commentary. Pp. 596; 8 plates. Vol. II, *Faessimile, Plates and Line for Line Hieroglyphic Transliteration.* Pp. 13; 22 plates.* Edited by JAMES HENRY BREASTED. Chicago: The University of Chicago Press, 1930. Price, \$20.00.

Index of Transactions of the American Otological Society, Vols. I to XVIII. Years 1872 to 1928, inclusive. Pp. 148. Published by the Society, 1929.

Het Kruis der Leprozen. By DR. DENIS MULDER. Pp. 135; 30 illustrations. Bandoeng, Java: Maks & vander Klits, 1930. Price, F. 1.50.

A description of 30 years' fight against leprosy in the Dutch East Indies. *Guy's Hospital Reports, Vol. 80, No. 3—July, 1930.* Edited by ARTHUR F. HURST, M.D. Pp. 378; illustrated. London: The Lancet, Ltd., 1930. Price, 12/6 net.

Standards for Maternity Care. Prepared by THE COMMITTEE ON MATERNITY CARE OF THE CHILDREN'S WELFARE FEDERATION and a COMMITTEE APPOINTED BY THE NEW YORK OBSTETRICAL SOCIETY. Pp. 31. New York: The Children's Welfare Federation, 1930.

These Standards were published in part in the American Journal of Obstetrics and Gynecology in the issue of July, 1930. Copies of the Standards may be secured from the Children's Welfare Federation, 244 Madison Ave., New York City.

Medical Care for 15,000 Workers and Their Families. With reports on certain phases of the organization by NELLIS B. FOSTER, M.D., RANSOM S. HOOKER, M.D., and MICHAEL M. DAVIS, PH.D. Pp. 23; 2 illustrations. Washington, D. C.: The Committee on the Costs of Medical Care, 1930.

This is the fifth publication by this Committee on a topic of great practical importance to the profession.

The Medical Clinics of North America, Vol. XIV, No. 2 (New York Number, September, 1930). Pp. 273; 73 illustrations. Philadelphia: W. B. Saunders Company, 1930.

NEW EDITIONS.

*Intestinal Tuberculosis—Diagnosis and Treatment.** By LAWRASON BROWN, M.D., and HOMER L. SAMPSON. Pp. 376; 124 illustrations. Second Edition. Philadelphia: Lea & Febiger, 1930. Price, \$4.75.

Elementary Zoölogy for Medical Students. By L. A. BORRADAILE, Sc.D. Pp. 397; 251 illustrations. Second edition. New York: Oxford University Press, 1930.

An abbreviation of the author's "Manual of Zoölogy," containing rather elementary descriptions of a few type animals such as the frog, a few protozoa, and worms, crayfish, cockroach, fly and mosquito, dogfish and rabbit.

Handbook of Anatomy. By JAMES K. YOUNG, M.D., F.A.C.S. Revised by GEORGE W. MILLER, M.D., F.A.C.S. Pp. 460; 154 illustrations. Seventh edition. Philadelphia: F. A. Davis Company, 1930. Price, \$3.75.

Minor Surgery and Bandaging. By GWYNNE WILLIAMS, M.S., F.R.C.S. Pp. 445; 262 illustrations. Twentieth edition. Philadelphia: F. A. Davis Company, 1930. Price, \$3.50.

A Text-book of Histology. By HARVEY ERNEST JORDAN, A.M., PH.D. Pp. 857; 596 illustrations. Fifth edition. New York: D. Appleton & Co., 1930.

In this edition, several figures have been improved by the substitution of new drawings, and minor changes have been made in the text on blood and endocrine tissues.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Sprue Treated With Liver.—WILKERSON (*South. Med. J.*, 1930, 13, 947) reports upon an individual who had sprue who was given liver as a therapeutic measure to control the disease. When this patient was first observed he was thin, emaciated and had a pronounced anemia, together with the stools that are characteristic of sprue. He was given an appropriate diet, to which was added liver and liver extract. In the first month, bowel movements were normal and the red count had increased pronouncedly. In three months he was to all intents and purposes well and the blood count had increased 2,600,000 red cells, or to normal figures. In discussing the pathogenesis of sprue, he suggests that there must be a similar deficiency in pernicious anemia and sprue—a deficiency which is made up by the liver. In one case it might arise because of the inability of the patient to eat; in the other instance because of the inadequate gastric digestion of protein.

Bacteriology of the Blood in Chronic Infectious Arthritis.—First Rosenow and then Cecil and his coworkers advanced the hypothesis, and attempted to substantiate it by experimental methods, that chronic arthritis is a result of infection and this infection is due to a definite bacterial agent which may be obtained from blood culture of individuals suffering from this type of disease. Cecil was able to get 61.5 per cent positive cultures of a Gram-positive micrococcus with the morphologic characteristic of streptococci. This organism injected into animals produced arthritis. MARGOLIS and DORSEY (*J. Infect. Dis.*, 1930, 46, 442) used a technique for cultures of the blood from arthritics that was of their own devising; they employed Cecil's modification of Clawson's method; they followed out Rosenow's technique and in a few cases cultured the blood in placenta broth. Ninety-two patients were observed, 89 of whom had chronic arthritis and 3 of whom had acute or subacute

rheumatic fever. Of the 89 patients, 49 had two parallel blood cultures by two different methods and 10 by three methods and the remaining 33 patients by one of the four methods. In only 5 patients were the cultures repeated. From 162 blood cultures streptococci were isolated in 4 instances by their own technique. Of the 68 blood cultures made by the method of Cecil, 3 cultures developed green-producing streptococci and 2 diphtheroids. The remaining 63 were sterile. Following the method of Rosenow in 11 instances, all the cultures were negative. One hundred and fifty-one cultures were sterile; 11 were positive, 6 with a green-producing streptococci, 3 with indefinite streptococci and 2 with diphtheroids. Their results are not comparable to those of Cecil and his group. Only a very small percentage of the cultures were positive, whereas with Cecil's there were well over 50 per cent positive. The final conclusion of these two authors that the occurrence of the organisms in the blood as well as in the joints of patients with arthritis suggests that these bacteria are of etiologic significance in this disease hardly seems justifiable in view of the bacteriologic studies that are reported in this paper.

Seasonal Variation in Efficiency of New Orleans Sunshine and Skyskine in Preventing and Curing Rickets in Rats.—MAYERSON and LAURENS (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 1070) report upon a large series of rats fed the Steenbock and Black rickets-producing diet, who were divided into groups, when weaned, and exposed to sunshine and skyskine for varying lengths of time. The controls showed florid rickets in five weeks. The test animals, on the contrary, when exposed to sunshine for three minutes did not develop the disease. During the winter months, an average daily exposure of ten minutes protected the animals, but five minutes did not. During the spring months, April and May, an average daily exposure of six minutes protected them. Exposure to skyskine necessarily was considerably longer. For example, during July exposure for twenty-four minutes was borderline, whereas forty-eight minutes afforded complete protection. These observations are of considerable interest. They confirm definitely that sunshine and skyskine are able to protect the experimental animal against rickets and they show that extremely short exposure is necessary in order to bring this about.

Frequent Chest Colds. Variability in Their Occurrence and the Bacteriology in Those Very Susceptible to This Type of Cold.—WALKER and ADKINSON (*Arch. Inter. Med.*, 1930, 46, 1) write that their paper deals with individuals who customarily have three or more chest colds a year over a number of years and who were studied at the time of the cold. They present a careful bacteriologic study of the flora isolated from the sputum of these patients. They show as a result of their study that there is considerable variability in the occurrence of chest colds in those who are susceptible, an individual characteristic not dependent on extraneous conditions. Many varieties of streptococci are found in sputum and this is the organism most frequently present. They hold because of this fact and because vaccines containing the most prevalent varieties of streptococci seem to prevent or benefit a cold in the chest that it is reasonable to assume that streptococci play a part in the causation of this common disorder.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

The Structure and Function of Articular Synovial Membranes.—SIGURDSON (*J. Bone and Joint Surg.*, 1930, 12, 603) state that the inner surface of articular capsules is not formed by a distinct membrane but by connective tissue modified as the synovial surface is reached. The cells here are more closely packed and the nuclei exhibit peculiar staining characteristics, but that does not seem to justify the use of the term membrane. The superficial synovial cells are not uniform in size or shape, some being quite small and round, while others are large with branching processes. Synovial villi vary greatly in size and shape and are composed of connective tissue resembling the part of the capsule from which they arise. The presence of stomata in articular capsules is not confirmed.

Changes in the Spinal Fluid Following Injection for Spinal Anesthesia.—LOSON, LEDEREN and STEINER (*Surg., Gynec. and Obst.*, 1930, 51, 76) say the pleocytosis (cell increase) would seem to indicate a certain amount of irritation of the serous lining of the subarachnoid space, but whether it was due to a general irritation of the whole extent of the dura or only of the immediate neighborhood of the puncture, it is impossible to say from these observations on the human subject. The increase in sugar, together with the increase in lymphocytes in the spinal fluid might be interpreted in the nature of mild encephalitis. However the absence of sequelæ in more than half of the cases studied, as well as the rapid disappearance and the mild character of symptoms present after spinal anesthesia would argue against this. Further studies are being made in which simultaneous blood and spinal fluid sugar determinations are being done, before and after, novcain injection, in order to observe if any relationship exists between the sugar content of the blood and spinal fluid under these conditions.

An Anatomical Study of Subdural Hemorrhage.—CHASE (*Surg., Gynec. and Obst.*, 1930, 52, 31) says that subdural hemorrhage is the important intracranial lesion in most cases of birth trauma. There is nothing to indicate that intradural hemorrhage or tentorial splits *per se* are of noteworthy clinical significance. The subdural hemorrhage is largely supratentorial and often bilateral. It is usually due to a stretching and rupturing of the small tributaries of the great cerebral vein near its junction with the straight sinus. Tentorial splits are relatively more numerous in the premature than in the full-term infant, partly because of the greater immaturity of fibers of the dural septa in prematurity. The causes of prolonged and difficult labor may be equally as important in these intracranial lesions as the operative interference. Signs of asphyxiation were constant but definite signs of intracranial irritation were recorded in only a small minority of cases.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

Clinical Investigations on the Comparative Effectiveness of Various Hypnotics by Oral and Rectal Administration.—FRIEDMANN (*Deutsch. med. Wchnschr.*, 1930, 56, 867) reports the results of a careful comparative investigation of a variety of hypnotics administered to adult males weighing between 60 and 70 kg. He attempts to determine an effective dose which will induce sleep during the day, as well as attempting to determine the rapidity and duration of action of the individual drugs and of certain combinations. Two grams of abasin proved highly sedative but not very effective as a hypnotic. It failed to produce sleep in 8 out of 20 patients, once following oral administration and 7 times following rectal. It required more than two and a half hours to induce sleep and the sleep lasted less than four hours. It is much less effective by rectum than orally. Much the same results are obtained from a combination of 0.3 gm. of bromural with an equal quantity of pyramidon, except that there is no essential difference in effectiveness between the oral and rectal administration of this combination. A single dose of 2 gm. of adalin is much more effective as a hypnotic. This failed to produce sleep in only 6 cases. The resulting sleep lasts up to seven hours and comes on within thirty minutes to several hours after administration. It is about twice as effective orally as rectally. Amylene hydrate proves to be an hypnotic of great value and is more effective by rectal than oral administration. A dose of 3 gm. produced effective sleep for four to eight hours in all but 2 of 16 patients, and sleep developed within one and a half to three and a half hours following administration. Potassium bromide behaves essentially as does abasin. Hydrated chloral proved to be the most satisfactory of all hypnotics studied. It is necessary, however, to watch its administration in order to avoid cumulative effects, especially chronic cardiac intoxication. It is equally effective orally and by rectum. A combination of 0.3 gm. of luminal with 5 gm. of urethane, theoretically, should be almost as effective as hydrated chloral, but clinical observation shows it to be chiefly sedative rather than hypnotic. Only 9 out of 25 patients obtained satisfactory sleep. This combination is best given rectally. Sodium barbital, in doses of 1 gm., is particularly effective as a hypnotic. In 21 out of 25 cases it produced sleep in from fifteen minutes to two hours. Since the gastric juice splits barbital sodium into barbital and sodium chlorid, it is better for oral administration to employ barbital and for rectal, barbital sodium. Noctal,

either in doses of 0.4 gm. orally in tablet form or rectally in suppositories, is a fairly effective hypnotic, but its action is not very trustworthy. A new preparation, novonal, is also only fairly effective. Sedormid, in doses of 2 gm., produces satisfactory sleep when given orally, but is merely sedative when administered by rectum. It should be a highly useful agent, but its cost is prohibitive. A combination of 0.5 gm. of barbital with 2 gm. of hydrated chloral, instead of proving more effective than each of these agents singly, proved distinctly less effective. Where prolonged continued sleep is required the administration every night of 2 gm. of sulphonal with 2 gm. of trional is effective, but sleep in the daytime is better secured by the administration of 1 mg. of scopolamin combined with 10 gm. of paraldehyd, the dose being varied to suit the patient. The most effective prolonged sleep, however, is to be secured from 1 mg. of scopolamin, 10 mg. of morphin and 0.4 gm. of sodium luminal administered subcutaneously. The resulting sleep is as effective as that obtained from avertin and is much more readily controlled. Avertin narcosis, however, is effective where prolonged sleep is desired, and it may later be replaced by noctal.

The Inactivation of Insulin.—An attempt has been made by SCHMIDT (*Klin. Wchnschr.*, 1930, 9, 1021) to determine where and how insulin is rendered inactive in the body. He reports in the present article the results of a variety of experiments. In the first group it is shown that insulin may be rendered inactive by incubation with finely-ground animal tissues. One gram of fresh muscle produces slight inactivation of 10 units of insulin; the same amount of ground spleen almost completely inactivates 10 units; kidney inactivates more than 10 units but less than 25 per gram, while liver destroys more than 25 units but less than 50. By suitable filtration of fresh, finely-ground tissue to remove the cells, a tissue juice is obtained in the form of glycerin extract. These extracts are found to be significantly weaker than the minced tissues but, like the former, they are capable of inactivating insulin when incubated with it.

Again, the extract of liver is found to be the most potent. Heating of these fluid extracts to 100° C. completely destroys their power of inactivation, indicating that it is due to some ferment. Acidification of the extracts also destroys their potency. Second in its capacity to destroy insulin is kidney extract, while extracts of lung and spleen are feeble and that of muscle is inactive. Although the precise chemical composition of insulin is not known, evidence points to its belonging to the protein group of substances as it is destroyed by the alkalis, pepsin and trypsin. From these facts the author reasons that the tissue ferments responsible for its destruction in his experiments belong to the group of proteolytic ferments known to be present in almost all tissues of the body. The injection of insulin into animals is followed by more rapid action when given intravenously than subcutaneously, but the toxic effects of insulin are more marked following the subcutaneous than the intravenous injection, indicating that, following intravenous injection, a large proportion of the circulating insulin is rapidly destroyed, probably in the liver, and others have shown that a dose of insulin is much more slowly destroyed in an animal the liver of which has been removed from the circulation than in an intact animal. In

closing, the author suggests that possibly in those cases of diabetes which it is difficult to control with even very large doses of insulin, there may be present an excessive amount of proteolytic ferment in the liver or other tissues which leads to very rapid destruction of the drug.

The Influence of Extract of the Anterior Lobe of the Pituitary in a Case of Dystrophia Adiposogenitalis.—It is a well-known fact that in dystrophia adiposogenitalis the metabolism is so altered that the usual specific dynamic action of protein is greatly reduced below that for normal individuals, along with other manifestations of the disease. J. T. PETERS (*Klin. Wchnschr.*, 1930, 9, 1219) gives in detail the results of the administration of anterior lobe extract hypophysis in a typical case occurring in a nineteen-year-old girl. Prior to the administration of this extract all forms of treatment were tried without avail. Promptly after the beginning of anterior lobe administration the patient's headache disappeared; muscular strength improved along with marked improvement in her gait. Menstruation which had not previously appeared also began. With these symptomatic evidences of improvement there was conclusive objective evidence in the rapid rise in the specific dynamic action of protein, as determined by metabolic tests. This rise reached the fully normal level. The author states that this is, so far as he could discover, the first instance of such a remarkable recovery and the first in which the relation between the specific dynamic action, the function of hypophysis and ovarian function in man have been demonstrated as definitely as these relationships have been in animals.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Poliomyelitis.—CAMPBELL and MIRSKY (*Arch. Ped.*, 1930, 47, 543) states that this disease has been known from the earliest times. During the twentieth century it attained epidemic proportions. The disease is caused by an invisible filter-passing virus which in the blood stream of recovered cases remains inert as it is held in combination by an immune body. This combination does not actually destroy the virus, which has extraordinary power to resist adverse living conditions. By the means of cataphoresis the virus can be dissociated from the immune body. Most cases of the disease are subclinical and escape diagnosis. The infection usually takes place during the early years. Second attacks have not been reported. General systemic invasion usually precedes but may occur coincidentally with the involvement of the nervous system. Poliomyelitis may be simulated clinically and pathologically by other diseases. The importance of diagnosis in the pre-paralytic stage is outstanding because the intramuscular injection of convalescent serum at this stage seems to prevent the development of paralysis.

Differential White Count in Infancy.—SMITH (*Am. J. Dis. Child.*, 1930, 40, 505) studied the differential white counts of 37 normal and sick infants from a supravital preparation and from fixed smears. In forty-three of forty-eight comparative smears the percentage of polymorphonuclear leukocytes was higher, and that of lymphocytes was lower in the living preparation than in the fixed film. The average of twenty-four counts from the group of normal infants showed the percentage of polymorphonuclear neutrophils to be 8.6 per cent higher in the supravital than in the fixed cover-slip smear and almost 12 per cent higher than in the slide. The lymphocytes, on the other hand, ran 14 per cent and 11 per cent higher in the fixed smears of the slide and cover slip, respectively, than the corresponding cells of the supravital preparation. The principal reasons for this discrepancy are unequal distribution of the cells and failure to identify and include all fragmented polymorphonuclear leukocytes in the differential count of the fixed smear. With the supravital technique the spread of cells is more even, trauma is reduced, and both motile and dying cells may be more readily identified. The lymphocytes have always been regarded as the predominant cell in the blood of the infant. This observation has heretofore been based on differential counts using the fixed smear with some form of the Romanowski stain. While counts made from the supravital film confirm the preponderance of lymphocytes over polymorphonuclear leukocytes, it is often by no means as marked as indicated in the fixed smear. The differential count from the fixed smear may unduly exaggerate the lymphocytic percentage and convey the erroneous impression of a blood dyscrasia. In pyogenic infections, especially when associated with a leukocytosis, the differential count from the fixed smears gives at times a much lower polymorphonuclear and a higher lymphocytic percentage than expected. That this discrepancy is often due to an increased fragility of the polymorphonuclear leukocytes is evident from comparative supravital studies. In a routine differential count from the fixed smear, particularly when it is employed as an index of the patient's resistance, the extent of white-cell damage observed on the slide should be noted. If fragmented cells have been included in determining the individual cell percentages, mention of this fact also should be made.

The Relation of Infection of the Ear and Intestinal Tract in Infants.—WISHART (*J. Am. Med. Assn.*, 1930, 95, 1084) reminds us that many authors believe that infection in the mastoid antrum is the cause of acute intestinal intoxication in infants. Study of the disease has been pursued for a period of five years, during the last two years of which a large body of observers have coöperated. The onset of the disease is rarely characterized by a cold. The great majority of infants were without any clinical evidence of upper respiratory infections at the time that they became toxic. Many infants remained without any clinical evidence of ear infection throughout the entire course of the illness. All accumulations or infections found in the mastoid antrums of infants at autopsy were antemortem in origin. Both ear drums of many showed abnormality immediately preceding death. This change

is an antemortem phenomenon due to forcible ejection up to the Eustachian tubes. When mastoid infection exists it is the result and not the cause of the child's lowered condition. Mastoid antrum puncture for diagnosis of latent mastoiditis is not without its dangers and is not to be recommended. Bilateral mastoid operations as a cure for the disease in this series was a failure. It is recommended that operation be postponed as long as possible. The autopsies of the 2 intensively studied series of cases of acute intestinal intoxication showed that mastoid infection was not common. There was no correspondence between the bacteriology of the infection in the upper respiratory tract and that in the intestinal tract. The author is attempting to gather evidence that will prove that the disease is of intestinal origin.

Menstrual Disorders in Adolescent Girls.—LAWRENCE (*J. Am. Med. Assn.*, 1930, 95, 1148) states that the occurrence of delayed menses or abnormal menstrual rhythm or flow in adolescent girls is indicative of subnormal development of the reproductive glands, which is likely to result in diminished fertility during adult life. It is more often due to systemic functional disturbances than to pelvic disease, and of these disturbances insufficiency of the anterior pituitary hormone is the commonest. Spontaneous compensation of such conditions does occur, and treatment is not indicated by slight delay in establishing normal menstruation, but if that function has not become normal by the sixteenth year, the attitude of optimistic expectancy must be abandoned. In the great majority of these adolescent patients, the symptoms are not due to primary ovarian insufficiency, but to some endocrine or non-endocrine systemic condition that renders the potentially normal ovary inert. The commonest of these conditions are focal infection, insufficient protein in the diet, and the insufficiency of the anterior pituitary hormone. In this series the oral administration of anterior lobe pituitary substance, in adequate dosage, gave encouraging results in patients in whom the existence of such a pituitary insufficiency was demonstrated.

The Leukocytes in the Blood of Children.—ERLICH (*Rev. Fran. de Ped.*, 1930, 6, 475) studied the blood of about 500 children, ranging in age from one day to fourteen years. He was endeavoring to determine the pathologic modifications of the leukocytes in various diseases. Leukocytosis, deviation to the left and toxic changes in the cells were found to be more or less important symptoms in the diagnosis of septicemia, erysipelas, pneumonia, ulcerative stomatitis, suppurative appendicitis, tuberculous meningitis, Heine-Medin disease, nontuberculous meningitis, typhoid, bacillary dysentery, acute colitis, scarlatina, measles, nontuberculous bronchial pneumonia, congenital and visceral syphilis, von Jaksch's anemia, pseudoleukemia, lymphosarcoma, granulomatosis, and severe alimentary intoxication. On the other hand no modifications of any note were found in tuberculous pleurisy and peritonitis, and various forms of anemia.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

ASSOCIATE IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Simple Method of Tubal Sterilization.—Many methods of sterilizing the female have been described and it has been said that every type of operation on the tubes has at some time failed of its purpose. The method which is described by BISHOP and NELMS (*N. Y. State J. Med.*, 1930, 30, 214) is one which they have used in 100 cases without having pregnancy follow in a single one, so that they feel that the technique is "safe, simple and secure." The operation consists of ligating a loop of the middle loose portion of the tube with *absorbable* suture material and resecting it. They use a double strand of No. 1 chromic catgut. No absorption occurs until the danger of bleeding has passed and when the ligature has been absorbed, the two cut ends of the tube draw apart, as they have noted in subsequent laparotomies. During this period the plastic exudate of the peritoneum has been thrown out and become organized and thus Nature throws a barrier of new peritoneum which becomes a permanent cover with no chance of fistula formation between the cut ends of the tube. They emphasize that they do *not* crush the tube for the crushed tissue may open a way for fistula formation and for the same reason nonabsorbable ligature material is not used, as it might slough through and leave a fistula which could reestablish the tubal lumen.

Vesicocervical Fistula.—The repair of a fistulous communication between the bladder and the cervix is often a very tedious and difficult operation on account of the depth of the lesion with the coincident poor exposure. In cases of this type GOTTLEB (*Zentral. f. Gynec.*, 1930, 54, 1090) has found that the treatment of the fistula by means of electrocoagulation gives very satisfactory results. While he first tried this method in cases of vesicocervical fistula it can also be used in cases of vesicovaginal fistula when the communication is of small caliber. The method is technically easy, safe, and causes so little pain that no anesthesia is necessary as a rule. Of course many of these small fistulas heal spontaneously but he believes that this method should be tried in cases where healing has not occurred after a period of six weeks. The method which he uses consists of the introduction of a cystoscope into the bladder in order to locate the vesical end of the opening, after which an electrode is passed through the cystoscope and into the fistulous opening as far as it will go. The fistulous tract is then coagulated in its entirety by slowly withdrawing the electrode with the current on. In this manner the epithelial lining of the fistula is destroyed and fresh granulations gradually fill in the tract, thus closing the artificial opening with consequent cure.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

Sudden Allergic Reactions Localized in the Antrum.—Stating that the appearance of polypi, of diffuse edema, and of similar filling defects commonly noted in radiographs of antrum, has long been regarded as a result of chronic inflammation, and in many quarters is considered sufficient evidence of hyperplasia to justify more or less radical operative interference, PROETZ (*Ann. Otol., Rhinol. and Laryngol.*, 1930, 39, 87) recounts 3 cases, from the study of which he concludes that the antral mucosa may increase to ten or more times its normal thickness during an allergic attack; a single sinus may be involved; the obliteration of the antrum as demonstrated by roentgenologic examination, is not necessarily hyperplasia, and allergy should be excluded before operation is undertaken; and that a mineral oil is the logical diluent for radiopaques to be used in allergic individuals.

Otosclerosis: A Metabolic Disorder.—Regarding otosclerosis as a metabolic disease analogous to osteomalacia and rickets in that a state of hypoparathyroidism obtains in all of them, MIRVISH (*J. Laryngol. and Otol.*, 1930, 45, 449) administered parathormone hypodermatically to three "otosclerotics." In one case the progress of the deafness was arrested and in the other 2 it was improved. The author states that rickets can be produced in two ways: either by a deprivation of vitamin D or by an excess of "calcovarín"—a substance he says he found in extracts of ovary, suprarenal cortex and "probably testis"—which reduces the blood calcium in characteristic manner both in rabbits and man. He also states that he encountered a similar rachitogenic factor in certain cereals, especially oatmeal.

The Rôle of Nasal Accessory Sinus Membrane in Systemic Infections and Toxemias.—LAWSON (*Ann. Otol., Rhinol. and Laryngol.*, 1930, 39, 159) believes that in sinusitis clinical manifestations are due usually to the absorption of toxins, although in some instances the sinus may act as a true focus of infection. He is in doubt as to whether the toxic material is absorbed from the sinus mucosa or from more of highly absorptive tissues which receive it. Uncomplicated sinusitis rarely produces severe constitutional symptoms. Low-grade, prolonged toxemia from sinuses may cause visceral degenerative changes. The author quite appropriately points out that the paranasal sinuses are "air-bearing" cavities and as such ventilation and not lavage should be the object of any surgical intervention in inflammatory processes. Wisely does he observe that with intelligent management most cases of sinusitis tend to recover.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

Present Status of Hysterosalpingography.—WITWER, CUSHMAN and LEUCUTIA (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 125) regard hysterosalpingography by means of lipiodol as a safe and simple procedure. In a series of 512 cases the only accident observed was that of a ruptured tube which led to no ill effects. The method is of great diagnostic value in developmental anomalies of the genital organs, in tubal affections leading to sterility, in certain very carefully selected cases of pregnancy in which therapeutic abortion is indicated or when a differential diagnosis from other obscure conditions is essential, in uterine tumors, excepting malignancies, and in certain extrauterine tumors. The contraindications are recent hemorrhage, inflammatory conditions that are not completely quiescent, active infections or malignancies involving the cervix, previous intrauterine interventions, ectopic gestation or uterine gestation in which a therapeutic abortion is not desired, infected cervical or uterine polyps and fever. In certain instances the injection of lipiodol is of direct therapeutic value.

Intravenous Method of Cholecystography.—In the experience of WATERS and KING (*Am. J. Roent. and Rad. Therap.*, 1930, 23, 34) with the intravenous injection of phenoltetraiodophthalein, the dye is comparatively nontoxic, for a few disagreeable reactions were encountered and none of these was alarming. The method of injecting the dye is not technically difficult nor unusually time-consuming, three injections being easily given in one hour. The cholecystograms are far superior to those obtained following the oral administration and the information gained from the films is more conclusive, because the intravenous administration insures the introduction of a definite amount of dye and is not complicated by factors of solution and absorption in the gastrointestinal tract. In addition, the liver function can be simultaneously determined.

Factors Determining Radioresistance in Tumors.—EWING (*Radiology*, 1930, 14, 186) holds that resistance of tumors to irradiation may be due to the adult character of the stroma; this form of resistance is observed in many types of sarcoma of bone, nerve and cartilage. The adult characters of epithelial cells and the substantial blood supply render adenomas and papillomas radioresistant. Carcinomas are resistant in inverse ratio to the degree of anaplasia and in direct proportion to the amount of desmoplastic reaction which they excite. In mixed

tumors in which one element is sensitive and the other resistant, the malignant portion may be sterilized, although the tumor does not diminish in size and a false impression of radioresistance may be gained; This is exemplified in mixed tumors of the testis and teratomatous tumors in the abdomen, kidney or sacral region. A special instance of spurious resistance is seen in very vascular giant-cell tumors, which are well designated as benign bone aneurysms. The nature of the tumor bed may favor or retard response to treatment; the high resistance of malignant tumors invading bone or cartilage is well known. Infected tumors which are the seat of exudative inflammation do not react well to treatment, but a full explanation of this fact is hard to find.

Roentgen Irradiation in Unresolved Pneumonia.—The suggestion is offered by MERRITT and McPEAK (*Am. J. Roent. and Rad. Therap.*, 1930 23, 45) that irradiation should be instituted in all cases of pneumonia showing definite Roentgen signs of delayed resolution three weeks after the onset. Of 7 cases thus treated by the authors, 4 cleared up entirely, 2 improved definitely and 1 was unchanged.

Advantages and Limitations of External Radiation in the Treatment of Rectal Cancer.—External radiation, in the opinion of BINKLEY (*Radiology*, 1930, 14, 207), constitutes the first step in radiation therapy of all rectal cancers, and in certain cases may be the only form of treatment necessary. The effect is limited by the depth of the tumor, the tolerance of the skin and the radioresistance of the cancer. External radium radiation is more effectual than high-voltage Roentgen rays. The two types of radiation may be combined advantageously.

Treatment of Malignant Growths of the Nasal Accessory Sinuses and Nasopharynx.—Radium and Roentgen rays are of value in treating this group of cases, according to QUICK (*Radiology*, 1930, 14, 191), but, except in palliative procedures, must be used in conjunction with surgery. Radium and Roentgen rays may be depended upon to eradicate the tumor tissue if applied accurately and uniformly throughout the growth in sufficient dosage. Surgery must be employed to provide exposure for radium application and adequate drainage. The anatomic relations are such that infection is a much greater menace here than in newgrowths in most other locations.

Treatment of Malignant Tumors of the Eye and Orbit by Radiation.—The present status of radiation therapy for tumors of the orbit is summarized by RODENBAUGH (*Radiology*, 1930, 14, 309) as follows: In tumors of the conjunctiva and cornea, radiation, preferably from radium, with a maximum conservation of normal tissue looking to clinical cure should be given first consideration. In basal-cell epitheliomas of the adnexa, as elsewhere in the body, the clinical cures are satisfactory and radiation is superior to other methods of treatment. The angiomas, lymphomas, sarcomas, granulomas, fibromas and nevi, occurring as primary tumors, are susceptible to radiation, their response varying with their histologic structure. The numerous metastatic tumors will vary in their response to radiation, their susceptibility depending on their histologic structure. Types of localized tumors of

the iris or ciliary body, of doubtful nature, have been favorably influenced by radiation, and such treatment should receive consideration before resorting to radical surgical methods. It is of greater importance to secure clinical regression of a newgrowth, with conservation of essential structures, than to have a histologic study, with loss of function.

Roentgen Diagnosis and Treatment of Thymomata.—In the view of DAUB (*Radiology*, 1930, 14, 267) too large a percentage of primary tumors of the thymus have passed unrecognized before autopsy. While the cases are uncommon they are not as rare as has been thought. The sarcomatous type of tumor predominates but a carcinomatous type of tumor also occurs. Roentgenologic examination of the chest will reveal the tumor as a more or less circular, sharply defined, nonpulsating mass occupying the anterior mediastinum. Roentgen ray therapy is indicated as soon as the diagnosis is made; the tumors are quite sensitive to radiation therapy and their prompt regression can usually be expected.

Results Obtained in the Treatment of Carcinoma of the Cervix Uteri With Radium and Roentgen Rays.—Reviewing 1094 patients treated during the decade from 1915 to 1924 inclusive, of whom 1001 were traced, BOWING and FRICKE (*Radiology*, 1930, 14, 211) find that in the small operable group, operated on and subsequently treated by irradiation, 75 per cent survived five years. Of the borderline cases, 61.53 per cent lived five years. In the inoperative group, 21.49 per cent of the patients were living after five years, and in a group previously treated elsewhere there were 24.82 per cent five-year survivals.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

Brown-Sequard Paralysis.—HASSIN, KENDRICK and CONNELLY (*J. Nerv. and Ment. Dis.*, 1930, 72, 245) present 2 cases, 1 occurring in a patient with syphilis, and one in a patient with poliomyelitis. The poliomyelitis case showed a motor paralysis of the left upper extremity with contralateral anesthesia. The sensory disturbance appeared in the form of syringomyelic dissociation and involved the entire right side of the body up to the level of the seventh cervical vertebra. He considers that this syndrome was caused by interruption of the long fibers of the spinothalamic tract. The case with syphilis exhibited paralysis of the left leg with disturbances of position sense, col-

lateral analgesia and thermoanesthesia up to the level of the sixth thoracic segment. Antiluetic treatment brought no relief and operation was resorted to, at which fibrous tissue was found over the dura at the level of the sixth and seventh thoracic segments (paeyhmeningitic in type). Following this there was remarkable improvement. The author discusses the prognosis in the second type of case and the advisability of operative procedure in those luetic cases which do not respond to chemotherapy, and so forth.

Psychologic Study of Accident Proneness.—FARMER (*Personnel Journal*, 1930, 2, 115) reports a study of accident proneness in relation to intelligence and sensory motor equipment. He finds a positive relation in that the 25 per cent of the subjects making the poorest scores showed an accident rate 2.5 times greater than that of the remaining 75 per cent. Also the accident rate of these subjects tended to increase with experience rather than diminish, as did the other groups. The same tests showed a similar relation to industrial proficiency, hence the author contends that the utilization of such tests for the selection of employees would increase efficiency in two directions: by decreasing accidents, and by the acquiring of more efficient workers.

The Prevention of Mental Deficiency by Sexual Sterilization.—ROBIE (*Psychiat. Quart.*, 1930, 4, 474) records a group of case studies indicating hereditary tendencies in mental deficiency, and discusses the possibilities of social control of this problem by means of segregation and sterilization, and concludes that sterilization offers a better mode of approach since segregation involves the housing of so many individuals that it is impracticable from a social and economic point of view. Since the sterilization operation in males is very simple, and the new method of sterilizing the female by intranterine cauterization of the uterus and the Fallopian tube through a hysteroscope, previous objections to the operative procedures are fairly well met. He believes that the constant carrying out of such a program would decrease the number of mental defectives as well as the amount of poverty, state dependency, prostitution, venereal disease and delinquency. He advocates the passing of sterilization laws in all states to permit the sterilization of mental defectives in state institutions as well as in selected cases outside of institutions.

A Clinical and Pathologic Study of Three Cases of Epidemic Encephalitis.—POOL (*J. Neurol. and Psychopathol.*, 1930, 11, 45) presents 3 cases in detail and attempts to correlate the clinical features and the pathologic findings. He argues that the only adequate explanation of the outstanding symptoms which constitute Parkinsonism is that of sympathetic decontrol due to interference with fibers of the rubrospinal tracts; that the symptoms of palilalia and sialorrhoea are probably the result of irritative phenomena due to degenerative products; and that the type of inflammatory cell encountered suggests that the disease is a manifestation of a chronic progressive encephalitis rather than a sequel to an acute infection. His argument is based on the comparison of the clinical pictures of Parkinsonism and lesions of the pyramidal tracts.

Psychosis Associated With Myxedema.—ZIEGLER (*J. Neurol. and Psychopathol.*, 1930, 11, 20) gives a fairly adequate review of cases of myxedema previously reported with mental symptoms, and reports 3 cases of his own. He considers that thyroid deficiency brings about a physiologic depression, which may precede abnormal mental states. On the whole, he believes the latter to conform more or less to the personality reaction of the individual patient rather than to follow any fixed clinical picture of mental disease. He finds great variation in the types of psychiatric manifestations. All of his patients improved on the administration of desiccated thyroid gland.

Biologic and Serologic Methods of Diagnosis in Epilepsy.—DE THURZO (*J. Neurol. and Psychopathol.*, 1930, 11, 36) reports in some detail a series of experiments in humoropathologic reactions in epilepsy. One of the more interesting findings resulted from an application to dementia præcox of a test for immune-hemolysin formation in inoculated animals. This reaction he calls "positive pleohemolytic reaction" and finds the highest titer occurring in dementia præcox when compared with other mental patients and healthy subjects. Applying a similar technique to epilepsy, convulsions were obtained in less than one minute, in 6 cases, after intravenous injections of 3 to 4 cc. of blood serum. In other cases intraperitoneal inoculation of blood serum was used and seizures did not occur but the body weight notably decreased. These findings substantiate those of Pagniez, Mouzon and Turpin. Blood serum warmed for ten minutes at 58° C. loses its toxic power. He finds slight changes in the bicolored mastic reaction, in the form of slightly irregular curves, and for this reason believes this reaction to be the most precise of all the colloid tests. In addition he has devised a China ink reaction of spinal fluid, rather simply carried out, which he finds positive in 87 per cent of the cases of epilepsy. The results of various reactions are published in the table accompanying the article.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

The Growth of Endometrial Autotransplants in the Rabbit.—Following the work of Sampson (1921) and Jacobson (1922) a great deal of interest has been given to the theory that portions of endometrium may become implanted upon the peritoneal surface. It has been generally accepted that in the human these transplants arise through the regurgitation of menstrual fluid through the Fallopian tubes. Several authors have undertaken the experimental reproduction of

endometrial implantation in lower animals. GLEAVE (*J. Path. Bact.*, 1930, 33, 675) found that the implantation of endometrium occurred with considerable ease in the rabbit. At times, however, adhesions formed at the site of implantation and multioocular or unilocular cysts of some size occupied the site. Ordinarily, however, the endometrial implants resembled the endometrium of the uterus of the same animal. Further, the endometrial changes observed in the uterine cycle were also to be observed in the implants. It was also noted that the endometrial implants were influenced by the ovarian hormone, estrin, in a manner similar to the uterine endometrium.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Will the Inhalation of Siliceous Dusts Activate a Partially Healed Focus of Tuberculous Infection?—GARDNER (*U. S. Pub. Health Rep.*, 1930, 45, 282) notes that it is usually thought that tuberculosis in cases of pneumokoniosis is an occupational infection; he believes, however, that the infection has occurred in the case of granite cutters prior to exposure to dust. The present study was made on guinea pigs which were infected by inhalation of a low virulence culture. This culture, used in this manner, produces a disease that tends to recovery. When exposed for prolonged periods to siliceous dusts the tendency to healing is lost and a distinctly progressive quality is observed in the lesions. The spread seems to be both by the air passages and through the blood stream—evidence of the latter being seen in the involvement of abdominal viscera. Microscopic examination confirms the adverse influence of the dust. The author admits that it is not at present desirable to carry the results on guinea pigs over to human pathology.

The Immunologic Significance of Colostrum.—SMITH (*J. Exper. Med.*, 1930, 51, 473) declares that the protective antibody content of normal cow serum is below that of colostrum of the same animal. The method used does not permit the titration of the actual amount of the antibody in serum. Quantities up to 2 cc. have no protective effect. The same limitations apply to the titration of milk owing to the introduction of large quantities of foreign protein into the peritoneal cavity of the guinea pig. When cows were immunized and a serum of high titer obtained, the antibodies in the milk of such cows rose to within the range of the method of testing. The relation of the protective capacity

ity of serum to that of milk was approximately 1 to 120 and 1 to 40 in the two animals. These figures do not differ much from those obtained by early investigators titrating the antitoxic content of serum and milk of animals undergoing immunization with diphtheria toxin. In the two experiments on calves, two and a quarter and eighteen days old respectively, fed a highly protective serum, no increase in agglutinins or protective antibodies could be demonstrated. The postponement of colostrum to the twelfth and eighteenth hour, respectively, did not prevent normal growth. SMITH and LITTLE (*ibid.*, 483) continuing these studies, under certain safeguards, such as isolation, raised calves from a large dairy herd by feeding normal and immune cow serum in place of colostrum. The losses were about 1 out of 10 in the later experiments. This outcome may probably be improved by the subcutaneous injection of serum during the first day. This loss may be no greater than that under ordinary conditions, since sporadic deaths among calves are not infrequent. However, no satisfactory statistics are available for comparison with results as given above.

The Extent of Gonorrhea and Syphilis in the United States.—A series of prevalence studies has been carried out in communities with a total population of more than 17,758,000 located in various parts of the United States, and representative of the population as a whole. It is estimated that there are in the whole country 643,000 cases of syphilis and 474,000 cases of gonorrhea constantly under medical care. Twenty-one per cent of the cases of gonorrhea and 40 per cent of the cases of syphilis are treated in public clinics. The combined case rate for gonorrhea and syphilis for the male population was nearly twice as high as that of the female, the rates being 9.65 and 4.85 per thousand, respectively. This difference was more pronounced for gonorrhea than for syphilis. Venereal diseases as a group far outnumber all other reported infections except influenza in times of an epidemic. The experience in the military forces of this and other countries in peace and in war time shows the venereal diseases to exceed any other condition as a cause of noneffectiveness. Among the second million men drafted during the World War, 56.7 per thousand were found by a casual clinical examination to have a venereal disease. It is estimated that in the continental United States there are 423,000 new cases of syphilis which seek treatment during the early stage (the first year) of the disease, and likewise, 679,000 new cases of gonorrhea each year which come under medical care during the first three months of the infection. This incidence represents an annual attack rate per 1000 population of 3.46 for syphilis and 5.71 for gonorrhea. PARRAN and USILTON (*J. Soc. Hyg.*, 1930, 16, 31), estimating 643,000 cases of syphilis and 474,000 cases of gonorrhea constantly under medical care in the United States, give case rates for gonorrhea 4.88 for males and 1.78 for females; and for syphilis 4.77 for males and 3.08 for females. Approximately 31 per cent of the total cases of venereal diseases under treatment are found among presumably indigent persons, inasmuch as this percentage of total cases were being treated at public expense in clinics, hospitals or other institutions. The peak-age group for the onset of both gonorrhea and syphilis has been determined as twenty to twenty-five years. A greater prevalence of venereal disease exists among the Negroes than

among the white population, the rate per 1000 being 8 for white and 11 for colored population. A recent study of the rural Negro in a southern state indicated that as high as 24 per cent of the entire population of more than one year of age showed a positive Wassermann reaction. The results of a number of published reports over a ten-year period indicated that of women admitted to maternity hospitals 6.9 per cent had a positive Wassermann reaction. General paralysis contributes 4 per cent of the population of our insane institutions. Syphilis stands first or second among the most frequently reported infections to the Public Health Service from the several state health departments. Gonorrhea stands about fifth. Among the general male population between the ages of fifteen and forty-five years it is estimated that the number of noneffective days lost through venereal diseases would approximate 21,000,000 days per annum, or a loss of approximately a half a day for each male of the United States between the ages of fifteen and forty-five years.

The Type Distribution of Meningococci in the United States During 1928 and 1929.—BRANHAM, TAFT and CARLIN (*U. S. Pub. Health Rep.*, 1930, 45, 1131) note that in 1928 and 1929 epidemic meningitis was more prevalent than at any other time since the World War, that it was highly fatal—50 per cent death rate and over in some localities—and that serum therapy was disappointing in results. The authors sought to determine whether the organisms differed from those found in earlier years. It was found that generally speaking 90 per cent of the cultures agreed with those found in earlier years, while 10 per cent were atypical.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 20, 1930

Preparation and Properties of Crystallized Alkali Salts of l-Cystine.—GERRIT TOENNIES and THEODORE F. LAVINE (from the Research Institute of the Lankenau Hospital, Philadelphia). l-Cystine, while insoluble in water, forms soluble salts with mineral acids and with alkali hydroxides. A method for the isolation of the alkali salts in crystallized form was found, consisting in treating cystine with a little less than the equivalent amount of alkali in methyl alcohol or in a mixture of water and ethyl alcohol, the composition being different according to the alkali (lithium, sodium or potassium) used, filtering from excess cystine, immediately precipitating by several volumes of acetonitrile or of a mixture of acetonitrile and ether, and allowing to stand for several hours before filtering. The sodium salt crystallizes with one molecule of water of crystallization. The potassium, as well as the

lithium salt, was observed in two different crystal forms. The specific rotation of cystine in solutions of its alkali salts is less than half as large as in an acid solution of the same concentration. However, by comparing acid solutions prepared from a salt and from free cystine, under equal conditions, practically identical values are obtained, proving that the substances described are simple salts from which the original cystine can be recovered unchanged. All three salts are very soluble in water; the solubilities in methyl and ethyl alcohol were determined quantitatively. The solubility in methyl is considerably larger than that in ethyl alcohol for all three salts. The solubility in the alcohols is largest for the potassium salt, less for the sodium, and smallest for the lithium salt. While aqueous solutions are stable for a number of days, the solutions in methyl alcohol begin to decompose, with formation of ammonia, almost immediately. The specific rotation of methyl-alcoholic solutions is almost three times as large as that of aqueous solutions. The solubility relations as well as the differences in stability and optical rotation between aqueous and alcoholic solutions suggest that the undissociated salt molecule is predominant in the alcoholic solutions.

Initial and Recovery Heat Production of Nerve.—D. W. BRONK (from the Johnson Foundation for Medical Physics, University of Pennsylvania). Employing recent improvements in thermopile and galvanometer design the course of the heat production of frog's nerve has been determined. Exceedingly accurate analyses have been obtained of the heat production resulting from nine to fifteen seconds stimuli showing a progressive increase in the rate of heat production during the period of stimulation. This is the sum of the heat associated with the conduction process and that accompanying the recovery therefrom. The recovery heat production is at a maximum rate immediately after the end of the stimulation and continues for some minutes at a decreasing rate. The duration of this recovery phase is largely dependent upon the temperature. At 19° C. it is about eleven minutes and at 24° C. about seven and three-quarters minutes. Seven experiments, comprising about seventy individual determinations, give the initial heat production as 8.9 per cent of the total. This is compared with the previous determinations by DOWNING, GERARD and HILL (*Proc. Roy. Soc. Biol.*, 1926, 100, 223) and GERARD (*J. Physiol.*, 1927, 62, 349) of about 11 per cent for frog's nerve and HILL'S (*Proc. Roy. Soc. Biol.*, 1929, 105, 153) recent value of 2.25 per cent for crustacean nerve.

A Study of Mammalian Fetal Movements, with Special Reference to the Influence of Narcotics.—ENGELBREKT A. SWENSON (from the Department of Anatomy, University of Pennsylvania). In all my previous studies on mammalian fetal movements it has been necessary for me to employ small amounts of narcotics. These drugs, when given in doses large enough to quiet the mother animal, either completely suppress or modify the muscular movements of the embryo or fetus. For these reasons they are not desirable.

Recently we have perfected a method which permits one to observe fetal movements in rats and guinea-pigs, for much longer periods of time than heretofore, and without using drugs to anesthetize the

mother. The new method consists of the production of anesthesia by cerebral compression, and is carried out as follows:

The skin and underlying tissue immediately over the occipital protuberance of the mother rat or guinea-pig are frozen with carbon dioxide. Through an incision made in this frozen tissue a small hole is made in the skull by means of a dental engine and burr. The degree of compression of the brain sufficient to produce general anesthesia is readily accomplished by inserting a small plug of absorbent cotton through the opening and gently forcing it into the space between the skull and the intact dura.

There is no indication of spinal shock and very little, if any, evidence of surgical shock in the mother. The quietness and composure of the mother permit of uninterrupted observation of the embryos or fetuses throughout the experiment. The mother and the young seem to suffer less from this procedure than from any other methods used heretofore. The effect of narcotics upon the embryo or fetus have been entirely eliminated.

Using as a norm the types and extent of fetal movements as observed in preparations in which the mother is thus anesthetized without drugs, it is now possible to study accurately the effects of drugs upon the active muscular movements of the embryo or fetus. Ether and chloroform, when given in exceedingly small doses to the mother, tend to increase the spontaneous movements of the fetuses. Cocaine and novocaine partially suppress some fetal movements, even when given as local anesthetics to the mother. Subcutaneous injections of magnesium sulphate into the mother, in doses large enough to quiet her, generally suppress all fetal movements. Sodium amytal, however, when given in doses large enough to completely anesthetize the mother, characteristically alters but does not completely suppress all muscular movements of the fetuses.

The study and analysis of the fetal movements have been made both by direct observation and with the aid of the moving-picture apparatus.

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INDEX.

A

- Abscess of Pott's disease, 295
 Acid-base equilibrium in human body, effect of food on, 123
 Actinomyces, pelvic, 731
 Action potential wave in nerve during and after oxygen lack, 145
 Adams, R. B., observations on chronic cholecystitis, 531
 Alimentary canal, medical treatment of spastic conditions in, 433
 hyperlipemia, 84
 Allan, Frank N., renal glycosuria, with ketosis during surgical complications, 670
 Analgesic effects of Roentgen rays, with especial consideration of bone metastasis in cancer, 736
 Anderson, Horace B., tumor of adrenal gland with fatal hypoglycemia, 71
 Anemia of dogs, feeding onions and, 744
 hypochromatic, treatment of reduced iron in, 724
 pernicious, cord symptoms in, failure of liver therapy in, 433
 erythropoiesis in, influence of gastric juice on, 809
 treatment of, with desiccated defatted stomach, 597
 with extract of fish liver, 603
 Anemias, classification of, on basis of differences in size and hemoglobin content of red corpuscles, 720
 Angina pectoris, treatment of, with muscle extract, 435
 Antibacterial action in cultures of penicillium, their use in isolation of *Bacillus influenzae*, 449
 Antrum, sudden allergic reactions localized in, 866
 Appendix, study of sympathetic nerves of, 447
 Argyll-Robertson phenomenon, 732
 pupil in polyneuritis, 292
 Arsenic findings in eczema and allied conditions in infants and young children, 288
 Arthritis, chronic infections, bacteriology of blood in, 857
 Ashe, Benjamin, transfusion of blood in Bright's disease, 476
 Asphyxia neonatorum, treatment of, modified Drinker respirator in, 583
 Asthma in children, 125, 436
 Atophan, action of, on hepatic excretion of uric acid, 124

Automobile exhaust gas, effect of repeated daily exposure of several hours to small amounts of, 594

B

- BACTERIOLOGY of blood and joints in chronic infectious arthritis, 300
 Ball, Fred E., some problems in diagnosis and treatment of thyrotoxicosis, 687
 Balyeat, Ray M., allergic migraine, 212
 Bárány symptom complex, 132
 Berkman, John M., anorexia nervosa, anorexia inanition and low basal metabolism rate, 411
 Bismuth arsphenamin sulphonate (bismarsen) in treatment of syphilis and other spirochete infections, 127
 Bitter, Ruth S., normal urine sugar in cystoscopic examination, 171
 Blackfan, Kenneth D., clinical and pathological studies on so-called tubular nephritis (nephrosis), 453
 Bladder, diverticula of, in women, 731
 Blepharospasm, treatment of alcohol injections in, 291
 Blood calcium, effect of bile salts on, 280
 human, inheritance and racial distribution of agglutinable properties of, 741
 hydration, plasma protein in relation to, 719
 platelets in newborn infants, 125
 transfusion of, in acute infectious diseases, 514
 in Bright's disease, 476
 Blood-sugar content of cataract patients, 131
 Bogan, M. E., size of the heart in goiter, 772
 Bone, hemangioma of, 738
 marrow, gelatinous degeneration of, 740
 solid, structural composition of, 143
 Bone-block operation for dropfoot, 578
 Bortz, Edward L., visceroptosis: clinical significance and treatment, 59
 Boston, L. Napoleon, gastric hemorrhage due to familial telangiectasis, 798
 Bowen, Byron D., acute interstitial pancreatitis in two cases of diabetic coma, 676
 Brain, metastatic abscesses of, 699
 Brain-liver weight ratio and infancy and childhood history of epileptics, 437

- Brams, William A., effect of amyl nitrite on size of heart and width of aortic shadow as determined roentgenographically, 618
- Brandau, G. M., sickle-cell trait in industrial workers, 813
- Brittain, Fannie Lou, allergic migraine, 212
- Bronchial obstruction, atelectasis, bronchopneumonia and lobar pneumonia and, 295
- Bronchiectasis, treatment of, multiple stage, lobectomy in, 282
- Brown-Sequard paralysis, 869
- C**
- CALCIUM therapy in adnexitis, 730
during childhood, 584
- Cancer, cervical irradiation in, results of, 731
of cervix, treatment of, results in, 587
of surgical, 289
of prostate, 121
of stomach, gastric secretion in, 119
- Carbon monoxid poisoning, treatment of, ultraviolet irradiation in, 581
- Carcinoma of small bowel, 579
- Cardiovascular disease, Roentgen ray diagnosis of, clinical value of, 591
- Castle, William B., observations on etiologic relationship of achylia gastrica to pernicious anemia, 305
- Cerebral circulation, 136
- Cerebrospinal fluid, distribution of nonelectrolytes between blood and, 446
"giant cocci" meningitis, unusual case of, 591
- Cheney, Garnett, value of blood bilirubin estimations in differential diagnosis of cerebrovascular accidents, 24
- Chest cold, frequent, variability in occurrence and bacteriology of those susceptible to, 858
- Chlorotic anemia of pregnancy, 818
- Cholecystitis, chronic, observations on, 53
- Cholecystography, intravenous method of, 867
- Chorionepithelioma, diagnosis of, biologic test in, 587
- Choroid plexus, papillomas of, 281
- Christie, Chester D., aneurysm of coronary arteries, 37
- Circulation, action of some newer drugs on, 283
- Cisterna magna pressure syndrome, 124
- Clinical investigation on the comparative effectiveness of various hypnotics by oral and rectal administration, 860
- Coburn, Alvin F., diabetic ketosis and functional renal insufficiency, 178
- Coccidioidal granuloma, 438
- College students, detection and treatment of personality difficulties, 299
- Colon, diseases of, factors of error in roentgenologic diagnosis of, 735
diverticulitis of, 431
- Colostrum, immunologic significance of, 872
- Conjunctiva, plasmoma of, in China, 440
- Connery, Joseph E., treatment of pernicious anemia with an extract of fish liver, 603
- Cox, Ralph L., aneurysm of coronary arteries, 37
- Crane, Martin P., effect of liver extract on blood of normal persons, 803
- Craver, Lloyd F., radiation therapy in polycythemia vera, 609
- Criminal justice, predictability in administration of, 298
- Crystallized alkali salts of l-cystine, preparation and properties of, 874
- Cutaneous irritants, list of, 288
- D**
- DEAFNESS of focal infective origin, 133
progressive, etiology of, 294
- Decerebrate rigidity, 447
- Dermoid cysts, complicated, treatment of, 290
- Dewis, E. G., flarimeter tests of circulatory fitness, 372
- Diabetes mellitus in children, 727
- Diaphragmatic hernia, nontraumatic, 135
- Dickey, Lloyd B., etiology of erythema nodosum in children, 489
- Diet, dental caries in young rats and, 280
- Differential white count in infancy, 863
- Diphtheria, circulatory failure of, 577
epidemiology of, in subtropics, 141
prophylaxis, new results in, 726
precutaneous, 434
- Diverticula of bladder in women, 731
of esophagus, 735
- Diverticulitis of colon, 431
- Dorst, Stanley E., bacterial hypersensitivity of intestinal tract, 650
- Dropfoot, bone-block operation for, 578
- Dystrophia adiposogenitalis, extract of anterior lobe of pituitary and, 862
- E**
- EAR and intestinal tract in infants, relation of infection of, 863
- Echinococcus involvement of bone, 591
- Elwyn, Herman, edema, 781
- Emetin, use of, in nonamebic abscesses of lung, 580

Encephalitis, epidemic, clinical and pathological study of, 870
 postvaccinal, 139
 Endemic typhus of Southeastern Atlantic States, experimental transmission of, by body louse, 743
 Endometrial autotransplants in rabbit, growth of, 871
 Entropion, spastic, treatment of, alcohol injections in, 291
 Epidermoid carcinoma of head and neck, metastasis and, 740
 Epidermophytosis of feet and epidermophytids of hands, 729
 Epilepsy, biologic and serologic diagnosis of, 871
 Epituberculosis, 824
 Ernstene, A. Carlton, erythrocyte sedimentation, fibrinogen and leukocytosis as indices of rheumatic infection, 12
 Erysipelas, ultraviolet radiation therapy in, 443
 Erythema nodosum in children, etiology of, 489
 Esophagus, diverticula of, 735
 Evans, Mary Jardine, preliminary note on bacteriologic studies and treatment of chronic epidemic encephalitis, 256

F

FARLEY, DAVID L., normal filament and nonfilament polymorphonuclear neutrophil count, 336
 Fatty degeneration of liver and kidneys in dog, diet and, 593
 Faulkner, James M., significance of sinus arrhythmia in old people, 42
 Fishberg, Arthur M., auricular fibrillation and flutter in metastatic growth of right auricle, 619
 Fitz, Reginald, problem of pulmonary tuberculosis in patients with diabetes, 192
 Food poisoning, *Salmonella enteritidis* and, 741
 Foord, Alvin G., acute interstitial pancreatitis in two cases of diabetic coma, 676
 Friedenwald, Julius, clinical study of gumma of liver, 656
 Friedgood, Harry B., ocular manifestations of sympathetic nervous system hyperactivity in conditions other than exophthalmic goiter and especially in essential hypertension. Lid-spasm: a new eye sign, 836

G

GAS bubbles in the anterior chamber: a differential diagnosis sign of metastatic *Bacillus coli* enophthalmitis in diabetes, 130

Gasserian ganglion, anesthetization of, relief of pain in absolute glaucoma and ciliary neuralgia and, 291
 Gastric symptoms, interpretation of, 444
 Gasul, Benjamin M., epituberculosis, 824
 Gatewood, subphrenic abscess, 398
 Gelatine, infants' dietary and, 287
 Gibbon, John H., Jr., prognostic value of initial leukocyte and differential count in lobar pneumonia, 31
 Gibson, Charles L., diagnosis of pneumococcus peritonitis from the blood picture, 344
 Gilman, P. K., remote symptoms of unrecognized thyroid adenomata, 405
 Goiter, size of heart in, 772
 Goldberg, Benjamin, epituberculosis, 824
 Goldhaft, Arthur D., production of hypertrophic arthritis by interference with the blood supply, 386
 Gonorrhea and syphilis in the United States, 873
 Gordon, A. H., low basal metabolism following lobar pneumonia associated with marked undernutrition, 695
 Graves' disease, pathogenesis of, 767
 treatment of, by injection of animal blood, 725
 Groat, William A., mitosis in myeloblasts in peripheral blood, 607
 Groyn, Norman B., some venous murmurs found in hepatic cirrhosis and their confusion with murmurs of congenital heart disease, 525

H

HAIR groupings in skin of Albino rat, 142
 Harvey, Earle A., uninfected mural thrombi of heart, 365
 Heart hormone preparation and extract of voluntary muscle, comparative studies of, 283
 Heath, Clark W., observations on etiologic relationship of achylia gastrica to pernicious anemia, 305
 Hejda, B., alimentary hyperlipemia, 84
 Hemangioma of bone, 738
 Herpes ophthalmicus febrilis with dendritic keratitis complicating therapeutic malaria, 440
 zoster, use of, solutions of pituitary in, 730
 Hinton, J. William, adrenalin test and cholesterol determination in diagnosis of borderline hyperthyroidism, 681
 Hitchcock, C. H., antistreptococcic serum treatment of patients with rheumatic fever, 497

Hodgkin's disease with involvement of bone and skeletal muscle, 735
 Howard, Isabel, effect of liver extract on blood of normal persons, 803
 Huntington's chorea without choreiform movements, 446
 Hurxthal, Lewis M., size of heart in goiter, 772
 Hydrogen and glass electrode, determination of pH of serum and, 142
 Hyman, Albert S., barium chloride in Stokes-Adams syndrome of complete heart block, 356
 Hypertension, so-called malignant, 719
 Hysterosalpinography, 586
 present status of, 867

I

IMMUNIZATION of chickens against fowl-pox, 138
 Influenza, epidemic of, in an isolated community, 594
 Infraclavicular foci of infiltration as evidence of incipient tuberculosis in young adults, 445
 Initial and recovery heat production of nerve, 875
 Insensible perspiration in infancy and childhood, 727
 Insulin, depressant action of, on genital organs, 581
 endonasal application of, 580
 inactivation of, 861
 Intestinal bacterial flora and microbe permeability, nutritional and meteorologic changes and, 138
 obstruction, uncomplicated high, cause of death in, 722
 Intranasal ultraviolet irradiation in nasal accessory sinus diseases, 134
 Intrathoracic exudates, calcification of, 443
 Intravenous urography by uroselectan, 133
 Irradiation in beauty shops, injuries resulting from, 736
 Isaacs, Raphael, treatment of pernicious anemia with desiccated defatted stomach, 597

J

JOANNIDES, MINAS, protective power of pleura, 833
 Jones, Noble W., observations on chronic cholecystitis, 531

K

KAY, W. E., remote symptoms of unrecognized thyroid adenomata, 405
 Kidney and ureteral lesions secondary to adnexal disease, 723

L

LANDON, JOHN FITCH, blood transfusion in acute infectious diseases, 514
 Lantin, Pedro T., analysis of 918 cases of bacillary dysentery treated with specific serum, 635
 Laryngeal nerves, action currents in, 294
 Lead therapy, 736
 Lecch, Clifton B., *Streptococcus viridans* endocarditis in children, 621
 Lemann, I. I., futility of alkali treatment of diabetic coma, 266
 Leprosy, 139
 recoveries from, 576
 skin immunity of certain anatomic regions from, 576
 Leukocytes in blood of children, 864
 Levine, Samuel A., uninfected mural thrombi of heart, 365
 Lewis, Paul A., obituary of, 146
 Lichen spinulosus following intradermal applications of diphtheria toxin, 438
 Liver, gumma of, clinical study of, 656
 Lung, abscess of, treatment of, 724
 gangrene of, treatment of, 724
 lymphogranulomatosis of, 304
 Lyddane, E. Stuart, lipoma of mediastinum, 79
 Lymphadenoma, etiology of, 739
 Lymphogranulomatosis of lung, 304

M

McEWEN, CURRIER, antistreptococcus serum treatment of patients with rheumatic fever, 497
 MacKenzie, L. F., flarimeter tests of circulatory fitness, 372
 Malaria as therapeutic agent for paresis, 136
 studies, control measures and, 301
 Mammalian fetal movements, influence of narcotics on, 875
 Marine, David, pathogenesis of Graves' disease, 767
 Mediastinitis, tuberculous, 738
 Menard, O. J., size of the heart in goiter, 772
 Ménière's disease, treatment of meatless diet in, 588
 Meningococci, type distribution of, in United States during 1928 and 1929, 744, 874
 Menstrual disorders in adolescent girls, 864
 Mental deficiency, sexual sterilization and, 870
 Metabolism of normal and leukemic leukocytes, 721
 Metastatic *Bacillus coli* panophthalmitis from calculus pyonephrosis, 292

Microcephaly radiogenic, 593
 Middleton, Richard, prognostic value of initial leukocyte and differential count in lobar pneumonia, 31

William S., influence of gastric juice on erythropoiesis in pernicious anemia, 809

Milk-borne septic sore throat and scarlet fever, 741

Morris, Roger S., bacterial hypersensitivity of intestinal tract, 650

Morrison, Theodore H., clinical study of gumma of liver, 656

Mosenthal, Herman O., transfusion of blood in Bright's disease, 476

Murphy, William P., effect of liver extract on blood of normal persons, 803

Murray, Cecil D., psychogenic factors in etiology of ulcerative colitis and blood, diarrhea, 239

N

NASAL accessory sinus membrane in systemic infections and toxemias, 866

sinuses and nasopharynx, malignant growths of, treatment of, 868

mucosa, effect of camphor, eucalyptol and menthol on, 441

Nephritis in childhood, 287

Nichols, John B., atrophy of subcutaneous fat associated with insulin injections, 90

Niles, Walter L., digitalis therapy in lobar pneumonia, 348

Nomland, Ruben, clinical study of 103 cases of scleroderma, 95

Novasurol, action of, on trichinosis in rats, 580

Nutrition of children on mixed and vegetable diets, 728

O

O'LEARY, PAUL A., clinical study of 103 cases of scleroderma, 95

Omentum, great, absorption and transference of particulate material by, 432

Orbital cellulitis in children, 733
 diagnostic problem in, 733

Osteogenesis of human periotic capsule, 293

imperfecta congenita, 448

Otitis media, acute suppurative, opening mastoid process in, 132

Otosclerosis, a metabolic disorder, 866
 blood groups and, 132

Otosclerosis in histogenic relations to osteodystrophia fibrosa (ostitis fibrosa), 293

and juvenile diseases of epiglottitis, analogies in picture in, 589

Ovary, endometrial cysts of, 130

Ovulation, time of, 439

P

PACK, GEORGE T., radiation therapy in polycythemia vera, 609

Palate, mixed tumors of, 138, 589

Palmer, Dounin L., observations on chronic cholecystitis, 531

Pancoast, Henry K., roentgenology of the thymus in infancy and differential diagnosis of enlarged thymus and its treatment, 745

Paralysis, Brown-Sequard, 869

Paranasal sinuses, repair of, following removal of mucous membrane lining, 442

Parker, Henry L., metastatic abscesses of brain, 699

Parotid gland, embryology, anatomy and surgery of, 721

Parsonnet, Aaron E., barium chlorid in Stokes-Adams syndrome of complete heart block, 356

Pasteurized dried fruits, 596

Pelvic actinomycosis, 731

Pemberton, Ralph, production of hypertrophic arthritis by interference with blood supply, 386

Percain, preliminary report on, 122

Peripheral vessels, action of camphor on, 434

Peritonsillar abscess, rational surgical relief of, 589

Peroral insulin of Stephan (cholosulin), investigations on, 284

Phagocytosis by bronchial epithelium in lungs of mice, 740

Phytobezzoan in stomach, 590

Pleura, protective power of, 833

Pneumocephalus, traumatic, 722

Pneumonia, chlorid retention in, 431

Poliomyelitis, 862

virus of neutralization of, by human sera, 280

Postoperative atelectasis, allergy and asthma in, 722

fat necrosis of breast, 120

shock, infusion treatment of, 121

Postvaccinal encephalitis, 139

tetanus, vaccination dressing and, 449

Pott's disease, abscess of, 295

Pregnancy, diagnosis of, value of a lateral view in, 590

Prophylactic value of convalescent and immune adult serums, 435

Prostate, cancer of, 121

- Psychiatric clinic, juvenile court and, 298
 Psychic factors in production of organic nervous diseases, 592
 Psychologic study of accident proneness, 870
 Psychosis associated with myxedema, 871
 Psychotherapy, schizophrenia and, 137
 Pulmonary infarction, clinical and roentgenologic consideration of, 737
 siderosis, 739

R

- RABINOWITCH, I. M., low basal metabolism following lobar pneumonia associated with marked undernutrition, 695
 Radiogenic microcephaly, 593
 Radioresistance in tumors, factors determining, 867
 Radium and Roentgen rays in treatment of carcinoma of cervix uteri, 869
 in treatment of disease with subcutaneous mucosal hemorrhages, 445
 Rectal cancer, external radiation in treatment of, advantages and limitations of, 868
 Reinhold, John G., new interpretation of van den Bergh reaction, 248
 Reisinger, John A., normal filament and nonfilament polymorphonuclear neutrophil count, 336
 Reviews—

- Alkan, *Organkrankheiten aus Seelichen Ursache*, 426
 Besredka, *Immunity in Infectious Diseases*, 113
 Blanton, *Medicine in Virginia in the Seventeenth Century*, 715
 Buckstein and Case, *Peptic Ulcer*, vol. x of *Annals of Roentgenology*, 273
 Camis, *Physiology of the Vestibular Apparatus*, 849
 Campbell, *Text-book on Orthopedic Surgery*, 852
 Chen and Schmidt, *Medicine Monographs*, Vol. XVII: *Ephedrin and Related Substances*, 851
 Cowdry, *Human Biology and Racial Welfare*, 276
 Crowe, *Handbook of the Vaccine Treatment of Chronic Rheumatic Diseases*, 852
 Curschmann, *Endocrine Disorders*, 571
 Davidson and Gullard, *Pernicious Anemia*, 804

Reviews—

- Davies, *Surgery of the Lung and Pleura*, 272
 Dawson, *Clio Medica*, Vol. I: *The Beginnings—Egypt and Assyria*, 570
 D'Herelle, *Bacteriophage and Its Clinical Applications*, 573
 Dodgson, *Report on Mussel Purification*, 573
 Draper, *Disease and the Man*, 572
 Ewing and Adrian, *Aphasia in Children*, 853
 Fearing, *Reflex Action: A Study in the History of Physiologic Psychology*, 425
 Fowler, *Tonsil Surgery*, 274
 Fraser, *Trauma, Disease, Compensation*, 274
 Goldbacher, *Hemorrhoids, the Injection Treatment and Pruritus Ani*, 116
 Graham, *Surgical Diagnosis*, Vol. I, 714
 Graham, *Surgical Diagnosis*, Vol. II, 850
 Gray, *Anatomy of the Human Body*, 712
 Guttmann, *Les Syndromes Dououreux de la Région Epipatique*, 113
 Harper, *Clinical Obstetrics*, 115
 Harrison, *Chemical Methods in Clinical Medicine*, 716
 Harvey Lecture Series, XXIV, 1928-1929, 272
 Hess, *Die Regulierung des Blutkreislaufes*, 275
 Hull, *Diseases Transmitted from Animals to Man*, 116
 Keller, *Modern Otology*, 276
 Kractzer, *Procedure in Examination of the Lungs*, 114
 Kugelmass, *Feeding in Infancy and Childhood*, 712
 Laroche, Fils, Saint-Girons, Rowe and Rowe, *Alimentary Anaphylaxis*, 574
 Levine and Schoenlein, *A Compilation of Culture Media*, 851
 Lyle and De Souza, *Manual of Physiology*, 849
 Marriott, *Infant Nutrition*, 425
 Maximow, *Textbook of Histology*, 852
 Myers, *Tuberculosis Among Children*, 275
 Negus, *Mechanism of the Larynx*, 117
 Nissen, *Practical Massage and Corrective Exercise*, 850
 Osborne, *What Everyone Ought to Know*, 572

Reviews—

- Outline of Preventive Medicine, 571
 Pack and Davis, Burns: Types, Pathology and Management, 716
 Power, *Clio Medica*, Vol. II, 716
 Rea, Affections of the Eye in General Practice, 569
 Reed, Tropical Medicine in the United States, 713
 Reinhold, Mühlens und zur Verth, Krankheiten und Hygiene der Warmen Länner, 717
 Rosenwaine, Science of Nutrition Simplified, 115
 Sante and Case, *Annals of Roentgenology*, vol. xi: The Chest, 569
 Stephenson, Incompatibility in Prescriptions and How to Avoid It, 574
 Toomey, Treatment of Skin Diseases in Detail, 273
 Turner, Personal and Community Health, 714
 Wells, Common Head Cold and Its Complications, 571
 Wieman, Introduction to Vertebrate Embryology, 715
 Rhinitis, intumescent, zinc ionization in treatment of, 135
 Richardson, Russell, normal urine sugar in cystoscopic examinations, 171
 Rickets in rats, seasonal variation in efficiency of New Orleans sunshine and skyshine in preventing and curing, 858
 Riddle, Matthew C., effect of single massive doses of liver extract in patients with pernicious anemia, 1
 Riseman, Joseph E. F., symptomatology of arterial hypertension, 47
 Roentgen diagnosis of lesions of jejunum and ileum, 738
 diagnosis and treatment of thyromata, 869
 irradiation in unresolved pneumonia, 868
 ray diagnosis and therapy of thyroid disease, 446
 therapy in acute inflammatory conditions, 296
 treatment of morbus Basedowii, 445
 Roentgenologic diagnosis in diseases of upper respiratory tract in children, 296
 manifestations of intracranial disease, 444
 studies of mastoid in infants, 135
 Roentgenology, halogenated oils and study of, 443
 Rudolf, R. D., observations on visceral pain, 558
 Rural school ventilation, study of, 451
 St. CLAIR, HUSTON, normal filament and nonfilament polymorphonuclear neutrophil count, 336
 Saprophytic fungi, sensitization of, 137
 Scarlet fever, epidemiology of, in subtropics, 141
 second attacks, 584
 Septic sore throat, 303
 Seward, Blanton P., clinical study of visceroptosis, 548
 Siliceous dusts, will inhalation of, activate a partially healed focus of tuberculous infection, 872
 Sinusitis, maxillary, dental caries and, 441
 Skin, diseases of ultraviolet ray therapy in, 590
 leprosy, immunity of certain anatomic regions from, 576
 lesions, radiant energy in, 297
 Smith, A. G., observations on visceral pain, 558
 Snider, Hiram F., new interpretation of van den Bergh reaction, 248
 Spinal anesthesia, changes in spinal fluid following injection for, 859
 Spine treated with liver, 857
 Staphylococci in food poisoning, rôle of, 431
 Starr, Isaac, Jr., circulation of the feet in diabetes mellitus with and without gangrene, 149
 Stenosing tendovaginitis at radial styloid process, 723
 Stewart, Winifred Bayard, preliminary notes on bacteriologic studies and treatment of chronic epidemic encephalitis, 256
 Stiehm, R. H., influence of gastric juice on erythropoiesis in pernicious anemia, 809
 Stomach, cancer of, gastric secretion in, 119
 phytobenzoar in, 590
 Strauss, Herman A., effect of amyl nitrite on size of heart and width of aortic shadow as determined roentgenographically, 618
 Strauss, Maurice B., chlorotic anemia of pregnancy, 818
 Streptococcal illnesses, chronic, 430
 Streptococci from scarlet fever, erysipelas and septic sore throat, 279
 Sturgis, Cyrus C., effect of single massive doses of liver extract on patients with pernicious anemia, 1
 treatment of pernicious anemia with desiccated defatted stomach, 597
 Subcutaneous tissues, effect of injection of gases into, 303

Subcutaneous tissues, injection of gases in, local effect of, 448
 Subdural hematoma, chronic, in infants, 286
 hemorrhage, anatomic study of, 859
 associated with tentorial splitting in newborn, 726
 Submucous fibrosis of bladder outlet in infancy and childhood, 126
 Swift, Homer F., antistreptococcus serum treatment of patients with rheumatic fever, 497
 Synovial membranes, articular, structure and function of, 859
 Syphilis, treatment of, bismuth in, 585

T

TEMPOROMAXILLARY subluxation, chronic recurring, 281
 Thompson, William P., leukopenia resembling agranulocytosis with recovery, 232
 Thymus disease, conditions simulating, and their diagnosis, 728
 Thyroid gland, goitrous enlargement of, due to amyloidosis, 579
 Tonsil, electrocoagulation of, 134
 modern aspect of anatomy of, in relation to germinal centers and lymphocytes, 734
 muscular attachments of, function of, 131
 Townsend, Wilnot C., observations on etiologic relationship of achylia gastrica to pernicious anemia, 305
 Traumatic pneumocephalus, 722
 Treponema pallidum, albino and brown breed of rabbit and, 303
 Tubal sterilization, simple method of, 865
 Tubercle bacilli in organs of reinfected rabbits, fate of, 595
 Tuberculosis in children, 437
 experimental epidemiology of, 450, 578
 pulmonary, treatment of, phrenic exsaisis in, 282
 specificity of light action in, 432
 spontaneous in guinea pig, 448
 Tuberculous infection in school children, a survey to determine prevalence of, 742
 mediastinitis, 738
 Tumors of bone, benign giant-cell, giant cells of, 739
 in chiasmal region, syndromes of, 592
 of eye and orbit, treatment of, by radiation, 868
 Typhus fever in United States, 302

U

ULTRAVIOLET therapy, change in blood of newborn following, 297
 Underweight children, increased growth by use of wheat germ, 285
 Undulant fever, etiology, epidemiology and laboratory diagnosis of, 743
 studies of, 141
 in Ware County, Georgia, 744
 Urethritis, nongonorrheal, 121
 Urinary surgery, indwelling ureteral catheters in, 281
 Uterine cancer, prognosis of, 439
 fibroids, Roentgen treatment of, 128

V

VACCINIA, studies of immunity, reactions and effects of heat, 140
 Van den Bergh reaction, study of, 144
 Vanzant, Frances R., renal glycosuria, with ketosis, during surgical complications, 670
 Vesicocervical fistula, 865
 Viosterol and cod-liver oil as prophylactic antirachitic agents, 125
 prophylactic and therapeutic dosage of, 583
 Visceral pain, observations on, 558
 Visceroptosis, clinical study of, 548
 Vitamins in experimental infection, action of large doses of, 725

W

WEISS, SOMA, symptomatology of arterial hypertension, 47
 Wells, P. V., flarimeter tests of circulatory fitness, 372.
 Whooping cough, early diagnosis of, 582
 by cough-plate method, 582
 Wilbur, Dwight L., multiple aneurysms of arteries of right arm, arteriovenous fistula and arterial embolism and, 221
 Willner, Otto, observations on mitral stenosis and measurements of normals among Chinese, 200
 Wolbach, S. Burt, clinical and pathological studies on so-called tubular nephritis (nephrosis), 453
 Wright, Lillie M., production of hypertrophic arthritis by interference with blood supply, 386
 Wyekoff, John, digitalis therapy in lobar pneumonia, 348

Y

YATER, WALLACE M., lipoma of mediastinum, 79
 Ylvisaker, L. S., flarimeter tests of circulatory fitness, 372

